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Die Forschung über die Wirkungen und Wirkungsweisen psychotroper Substanzen hat in den letzten Jahren einen unerhörten Aufschwung genommen. Was vordem nur ein erwünschtes Ziel war, ist zu einer neuen Wissenschaft geworden: Psychopharmakologie. Da eine fruchtbare Analyse und Synthese ihrer Probleme nur durch Zusammenarbeit aller Grundfächer (Pharmakologie, Neurochemie, Neurophysiologie, Neurologie, Psychologie und Psychiatrie) möglich wird, ist die Psychopharmakologie eine verbindende, integrierende Forschungsdisziplin. Die ständig anwachsende Literatur dieses komplexen Arbeitsgebietes ist jedoch bisher zwangsläufig über zahlreiche Zeitschriften verstreut, da es bis heute kein Spezialorgan gab, das sich ausschließlich der Psychopharmakologie widmet. Diesem dringenden Bedürfnis zu begegnen, hat sich eine Gruppe von Vertretern der verschiedenen Arbeitsrichtungen der Psychopharmakologie entschlossen, eine neue Zeitschrift „Psychopharmacologia" zu gründen. In ihr sollen die bedeutenden Fortschritte dieses Arbeitsgebietes durch Veröffentlichung experimenteller und klinischer Originalarbeiten, Übersichten der neuesten Literatur sowie kurzer Originalmitteilungen zusammengefaßt werden.

Recent years have witnessed an unprecedented advance in research on the action and effects of psychotropic drugs, and what, formerly, was just a distant goal, has now evolved into a new branch of science: psychopharmacology. As, however, any fruitful analysis and synthesis of its problems can only be attained with the aid of the complete scale of basic sciences (pharmacology, neurochemistry, neurophysiology, neurology, psychology and psychiatry), psychopharmacology constitutes an integrating discipline of research. Owing to the lack of an organ devoted especially to psychopharmacology, the constantly increasing literature pertaining to this complex field of activity has hitherto of necessity been scattered among various periodicals. In order to overcome this drawback, a group of representatives of the various psychopharmacologic sections have engaged in editing a journal, „Psychopharmacologia", in which the publication of original experimental and clinical papers, reviews of recent literature and short original notices will provide a comprehensive survey of the important progress which is being actually achieved in this field of science.

Ces dernières années ont vu un développement sans précédent dans la recherche des effets et du mode d'action des substances psychotropes sur le «Comportement» et ont fait naître une nouvelle science: la Psychopharmacologie. Comme ces problèmes ne peuvent être résolus que par la collaboration des disciplines de base telles que la pharmacologie, la neurochimie, la neurophysiologie, la psychologie et la psychiatrie, la psychopharmacologie est devenue un champ de recherche de première importance. Cependant la littérature toujours croissante en ce domaine de recherche est forcément disséminée dans de nombreux périodiques, puisqu'il n'existe pas encore de journal exclusivement consacré à la psychopharmacologie. Pour répondre à ce pressant besoin un groupe de représentants des diverses disciplines de la psychopharmacologie s'est mis en devoir de rédiger un nouveau journal dans lequel seraient rassemblés les progrès importants de ce domaine, par la publication d'ouvrages originaux expérimentaux et cliniques, ainsi que des rapports sur des questions actuelles.

Richtlinien für die Mitarbeiter siehe am Schluß des Heftes. — Directives to Authors are given at the end of this number. — Directives destinées aux auteurs, voir à la fin du fascicule.

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Behavioral Pharmacology

By

MURRAY SIDMAN

With 4 Figures in the Text

(Received August 5, 1958)

Pharmacologic agents that exercise effects upon behavior have been known since antiquity. But intensive and systematic efforts to investigate the relations between drugs and behavior have only recently begun. A major factor contributing to the slowness of development of a science of Behavioral Pharmacology was the late recognition that behavior is a phenomenon amenable to study by the methods of Natural Science. The overt behavioral effects of drugs were disguised, in conformity with general psychological practice, by such terms as "alertness", "stimulation", "euphoria", "sedation", and, more recently, "tranquilizing". These and other supposedly descriptive terms provided a catchall classificatory scheme in which to deposit a bewildering variety of behavioral observations. They served to impose a beguiling but false veneer of simplicity upon the behavioral changes associated with the administration of chemical agents. Behavior disorders are difficult enough to describe at the human level, and in animals, with which we share neither a common verbal intercourse nor a common behavioral topography, a description in terms of the traditional classifications is virtually imposible. It is apparent that the less precise our behavioral specification, the less precise will be our knowledge of the relations between drugs and behavior. Furthermore, decreased descriptive precision will inevitably be accompanied by increased claims for the effectiveness of a given drug in influencing behavior.

The advent of tranquilizing drugs, accompanied by assertions that they serve to ameliorate behavior disorders, has focussed attention upon the need for more precise specification of behavior and behavioral processes. This is particularly true at the preclinical level, where, fortunately, experimental psychology has produced some of its most striking developments in the past few decades. Behavioral Pharmacology, profiting from recent advances in both Psychology and Pharmacology, has now extended to the study of other types of drugs than tranquilizers, and employs an ever-widening range of behavioral techniques. An excellent historical

summary of preclinical research on drug-behavior relationships has been provided by BRADY (1956 c) and this review will, therefore, be confined to recent developments.

Operant conditioning techniques

A basic requirement in the assessment of drug-behavior relationships is an experimental repertoire of reproducible behavioral baselines from which to measure drug-correlated changes. Furthermore, reproducibility in terms of averaged data from a group of experimental subjects is not sufficient. Because of the great quantitative variability in dose-response effects from one subject to another, averaged data are likely to obscure, or even falsify, the effects of a drug in the individual organism. Also, the use of statistical control in testing the effects of drugs implies a lack of experimental control over behavior that bodes ill for a program of research on such a complex subject-matter as drug-behavior relationships.

The most precise, sensitive, and reproducible techniques for controlling the behavior of the individual subject are those that have been developed over the past 25 years by B. F. SKINNER, his co-workers, and others who have extended the techniques in various directions [SKINNER (1938), FERSTER and SKINNER (1958), BRADY and HUNT (1955), KELLER (1941), BLOUGH (1955), SIDMAN (1953), GUTTMAN and KALISH (1956), FERSTER (1953)]. The methods are based upon a simple principle; namely, that the characteristics of behavior are, to a large extent, determined by the environmental events that have been consequent upon past occurrences of the behavior. Behavior that operates upon the environment has been termed "operant behavior", and the process of manipulating such behavior by means of its environmental consequences has been termed, "operant conditioning" [SKINNER (1938)]. Reproducibility among subjects within a given species, and between species, has been enhanced by selecting, for measurement and manipulation, a response whose topography is congenial to the organism, and one that the organism can perform and immediately be in a position to repeat; by selecting an environmental consequence, or "reinforcement", that is appropriate to the particular individual; by limiting the experimental environment; and by utilizing motivational levels that are strong enough to override many experimentally irrelevant variables. For example: the subject may be a hungry pigeon, pecking at a lighted spot on the wall, and reinforced by a small amount of grain; or a thirsty rat may press a lever, thereby obtaining a small drop of water; or a monkey may press a pedal, the consequence of which is postponement of shock. The object is not the study of eating or drinking behavior *per se*, or of pain. The purpose of these techniques is to place an arbitrary sample of behavior under experimental control so that *behavioral processes* may be investigated as a function of various operations.

Non-specific effects

Many types of behavioral baselines have been developed against which to measure the effects of pharmacologic agents. But before describing investigations that have been directed at the evaluation of specific drug-behavior relationships, it will be useful to examine some more general problems that arise whenever overt behavior is employed in an assay technique. These are the problems of general excitatory or depressant effects, motor debilitation, sensory deficit, and motivational effects. For example, if a given drug abolishes behavior whose function it has been to avoid an electric shock, can we draw the conclusion that the drug is specific to this type of behavior? Is it safe to classify the drug as an anxiety reducer? The possibility exists that the drug would have produced a depressant effect upon any type of behavior that had been used as a baseline. Or perhaps the subjects were so debilitated that all motor behavior was virtually impossible, thus invalidating any inference in terms of a particular type of behavior.

One method of meeting such problems has been to provide the experimental animal with a behavioral repertoire, any component of which can be elicited at any time. Then a given drug may be tested over a spectrum of behavior in the same animal at different times. An excellent example has been provided by DEWS (1956), working with pigeons. In the procedure employed by DEWS, two types of behavior were placed under stimulus control by means of a variant of FERSTER and SKINNER's "multiple schedule" technique. The birds were rewarded with grain for pecking at a lighted key. When the key was red, 60 pecks were required to produce the grain, and when the key was blue the bird was rewarded for the first peck made after 15 minutes had elapsed since the preceding reward. Thus there were two reward schedules employed. A *fixed ratio* of 60 pecks per reward was required in the presence of the red key. In the presence of the blue key, reward was based upon responses emitted after the passage of a *fixed interval* of time. Under appropriate deprivation conditions, the fixed ratio and fixed interval reward schedules typically generate markedly different rates and temporal patterns of responding, as is illustrated in section D of Fig. 1. On the fixed interval schedule there is no response at all at the beginning of the interval, and then there is accelerated responding up to receipt of the reward. The fixed ratio performance is characterized by high, sustained rates.

Fig. 1 shows the time course of action of phenobarbital sodium, as reflected in the fixed ratio and fixed interval behavior. Three hours after injection (section A) there was almost no pecking behavior on the fixed interval schedule. While the fixed ratio behavior was severely disturbed, there was still a substantial output. It was thus economically demonstrated that the drug did not exercise a general depressive effect upon all behavior. HERRNSTEIN and MORSE (1956) have confirmed this

finding with pentobarbital by means of an experimental arrangement in which the ratio and interval behavior were blended into a single, smooth performance. Sodium pentobarbital acted to fractionate this performance, selectively eliminating the fixed-interval behavior and leaving the rapid fixed-ratio component of the response rate untouched.

Sections B and C of Fig. 1 demonstrate a second method of determining the specificity of drug effects upon behavior. Section B, 24 hours

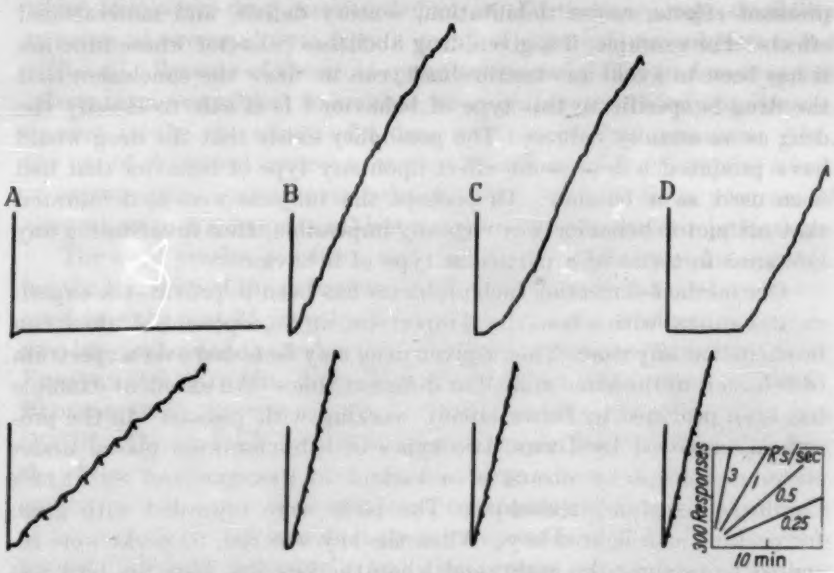

Fig. 1. The effects of phenobarbital on performance at various time intervals after injection. Responses are recorded cumulatively as a function ot time. A = 18 hours after injection, B = 24 hours, C = 36 hours, and D = 48 hours. The upper series shows the interval behavior, and the lower series shows the corresponding ratio behavior. The performance in Section D is essentially normal. [From DEWS (1956)]

after injection, shows a high rate of pecking on the fixed interval performance, but the temporal pattern of responding is markedly different from normal. The bird pecks irregularly throughout the whole interval, with no sign of the initial pause. The ratio behavior is essentially normal at this stage. BOREN has reported a similar effect with benactyzine. On the fixed interval schedule, benactyzine allowed responding throughout the interval and, as a result, caused an over-all increased rate. Chlorpromazine decreased the over-all rate and somwhat lengthened the pause after reinforcement, while adiphenine produced no noticable change. HERRNSTEIN and MORSE (1957) have reported a quantitative technique for measuring the curvature in the cumulative record of fixed-interval performance, and have shown that their "quarter-life" measure is sensitive to the effects of pharmacologic agents. These data demon-

strate that a drug effect need not appear in the form of a simple depressant or excitatory action upon behavior. The consequence of drug administration may be a shift in the *pattern* of behavior, with over-all changes in response frequency only indirectly reflecting the new temporal pattern. When the consequence of drug administration is a change in the pattern of behavior, rather than an all-or-none depression or excitation, the problem of general debilitating effects is largely circumvented.

There are other dangers inherent in an approach to drug-behavior relationships that would take as its datum an all-or-none change in frequency or probability of occurrence of a response. DEWS (1955a) has shown, for example, that pentobarbital may completely depress behavior on both fixed interval and fixed ratio reward schedules. But the dose-response curves are markedly different for the two types of behavior. Fixed-ratio performance is considerably more resistant to pentobarbital than is fixed-interval performance. A relatively low dose of pentobarbital that almost completely depresses fixed-interval behavior may actually increase the response rate on a fixed-ratio schedule. In addition to dose-response effects, there may be differences in the way various types of behavior are affected by a drug as a function of time. Fig. 1 demonstrates that the apparent time course of action of phenobarbital is strongly modified by the reward schedule employed to maintain the baseline behavior. In evaluating the specificity of a drug effect, therefore, a family of dose-response curves, determined over a wide range of time intervals following drug administration, is the only sure method of preventing overgeneralization. There have, as yet, been few published studies that possess such a high degree of inclusiveness. DEWS (1956), however, has suggested, on the basis of data that deal with the effects of phenobarbital and meth-amphetamine on behavior generated by multiple fixed interval-fixed ratio reward schedules, that the sequential changes at various time intervals following a single large dose of a drug are equivalent to to those caused by graded doses at a constant time interval. If further research proves this finding to be generalizable to other drugs and other types of behavior, the difficulties in studying drug-behavior relationships will be greatly reduced.

The possibility of sensory deficit, i.e., drug effects upon the discriminative capacity of the organism, is not only worthy of study for its pharmacologic implications, but also poses a technical problem when multiple procedures under stimulus control are employed to generate behavioral baselines. For example, SIDMAN (1956) reports an experiment in which a rat was trained to press a lever for a water reward according to three reinforcement contingencies, each under stimulus control. When a clicking noise was presented, 10 lever presses were required to produce the reward. The typical high rate of responding was observed under

this *fixed-ratio* schedule. If a tone was present, lever pressing responses were reinforced only when 30 seconds or more had elapsed since the preceding response. When *spaced responses* were thus required, the customary low rate of lever pressing (WILSON and KELLER) was observed. When neither the tone nor the clicker was present, a *variable-interval* schedule was in effect, in which responses were rewarded at irregular time intervals. This schedule generated a rate of response intermediate between the fixed ratio and spaced responding performances. Administration of reserpine abolished the differential performance on the three schedules and brought the variable-interval and fixed-ratio rates down to the level normally maintained under the requirement of spaced responding. The problem now arises as to whether the drug affected only the ratio and interval behavior while leaving the spaced responding untouched, or whether the animal, under the influence of the drug, simply could no longer discriminate among the three stimulus conditions. One method of determining the answer to such a question is to obtain dose-response and time-course data. If the several types of behavior display different dose-repsonse curves, or if the time course of action of the drug is different for each behavior, as was the case in SIDMAN's (1956) experiment, then the behavioral changes are less easily attributable to a loss of discriminative capacity.

A more direct procedure is to make an explicit study of the effects of drugs upon discriminative capacity. DEWS (1955 b) initiated a study to determine whether a number of drugs alter the pigeon's capacity to discriminate between the two key lights. He found that the behavioral control exercised by a simple pair of stimuli was not appreciably affected by the drugs, but that when more complex conditional discriminations were required, clear discriminative deficits appeared. Similar studies have been carried out by BLOUGH (1957). In BLOUGH's technique, the pigeon was presented with two response keys, separated by a vertical bar. The keys and the bar could be independently illuminated. Hungry birds were rewarded with food, on a variable-interval schedule, only when they pecked the correct key. The correct key was cued as follows: If the vertical bar was lighted, pecking on the darker of the two keys caused food to be presented to the bird. If the bar was dark, pecks on the brighter key brought food. Thus, the pigeons had to discriminate not only between bright and dark keys, but their choice was conditional upon the illumination of the center bar.

BLOUGH presented two measures of the drug effects. One of these was the total number of responses emitted by the birds, and the other was the percentage of the responses that were correct. Fig. 2 illustrates the effects of LSD-25 upon these measures, expressed as deviations from control performance. It may be seen that LSD-25, soon after administra-

tion, produces a *decline in total responses* but an *increase in accuracy*. There is a clear effect of this drug upon complex discriminative behavior, an effect that was not apparent from the measures of total output. BLOUGH found, in addition, that chlorpromazine *decreased both accuracy and output*; that pentobarbital *decreased accuracy* and *increased output*; that meperidine, like chlorpromazine, *reduced both accuracy and output*;

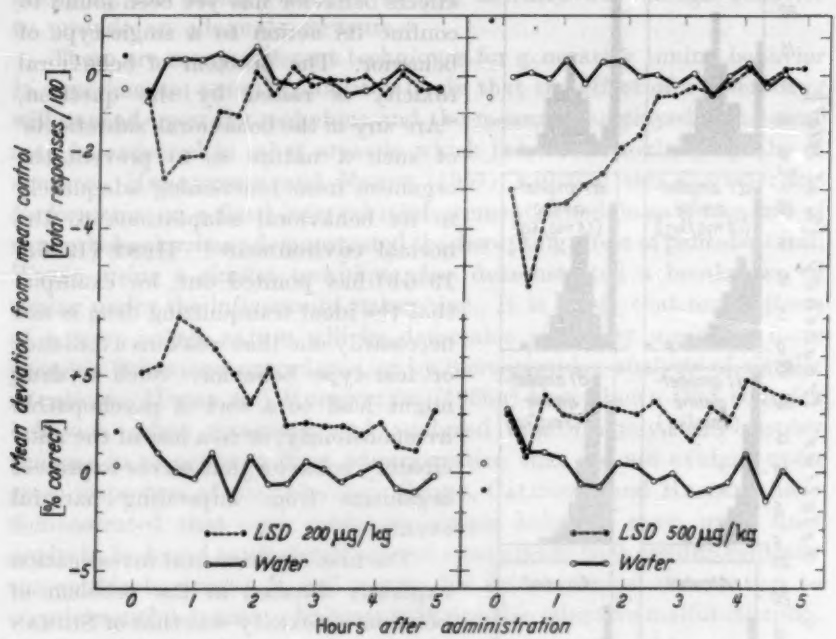

Fig. 2. Total responses and percent correct responses in a conditional discrimination. Performance is plotted as a function of time following oral administration of LSD-25. [From BLOUGH (1957)]

and that caffeine had little effect upon either measure. In another study, BLOUGH (1956) also demonstrated that both alcohol and sodium pentobarbital *increase* the total response output while decreasing the accuracy of the discrimination. Differences in the time course of action also appeared not only among the drugs, but, in some cases, beween the two measures for a given drug.

It should be emphasized that a drug effect can be attributed to a loss of discriminative capacity by the organism only if the two or more types of behavior in a multiple schedule procedure fail to display a differential response to the drug. When each of the behavioral members of a multiple baseline reacts similarly to the drug, then it becomes necessary to employ techniques, such as those of DEWS (1955b) or BLOUGH (1956), for a direct test of stimulus discrimination.

Behavioral toxicity

A problem closely related to non-specific behavioral effects is that of behavioral toxicity. While physiological toxicity has long been recognized as a major problem in the evaluation of any drug, the corresponding behavioral problem has only recently been explicitly stated. No drug that affects behavior has yet been found to confine its action to a single type of behavior. The problem of behavioral toxicity is raised by the question, "Are any of the behavioral 'side effects' of such a nature as to prevent the organism from functioning adequately in its behavioral adaptations to the normal environment?" HUNT (1956a, 1956b) has pointed out, for example, that the ideal tranquilizing drug is not necessarily one that weakens avoidance or fear-type behavior. Such a drug might lead to a sort of psychopathic irresponsibility, or to a loss of the anticipatory behavior that serves to protect organisms from impending harmful events.

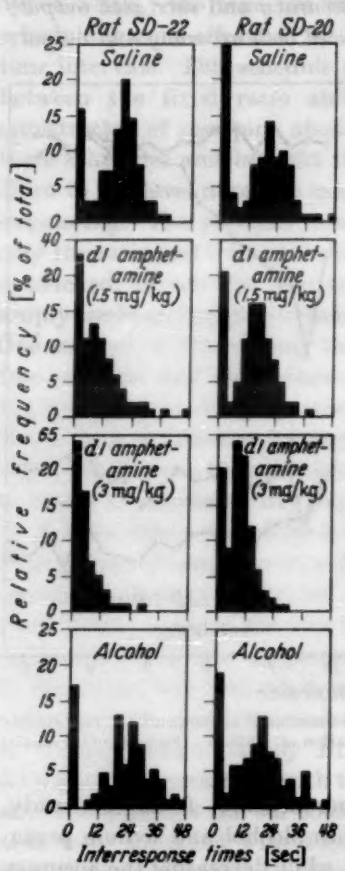

Fig. 3. Relative frequency distributions of the time intervals between successive lever presses. Each distribution represents one animal's performance in a single two-hour session. [From SIDMAN (1955)]

The first experimental investigation explicitly directed at the problem of behavioral toxicity was that of SIDMAN (1955), who utilized the technique of WILSON and KELLER to determine whether amphetamine had any effect upon temporal orientation. White rats were rewarded for lever pressing only when they spaced their lever pressing responses at least 20 seconds apart. The temporal pattern of responding that develops with this procedure may be seen in the "saline" records of Fig. 3. The relative frequency distribution of time intervals between successive lever pressing responses rises sharply to a peak at 16—20 seconds, indicating relatively well-developed timing behavior. Amphetamine, in increasing doses, shifted the peak of the distribution toward the shorter values, indicating that the animals were responding too early. The orderly shift in the temporal patterning of responses indicates that the effect of the

drug was not a simple excitatory one, even though rate increases were also observed. The effects of alcohol, sodium pentobarbital, and reserpine were also tested against a baseline of spaced responding, and markedly different effects were observed in each case [SIDMAN (1956)]. Sodium pentobarbital, unlike amphetamine, completely destroyed all evidence of timing. While responding was eventually completely suppressed by reserpine, the timing remained as long as there was enough behavior to provide an adequate measure.

There are many different techniques for generating timing behavior in experimental animals, and it is likely that the effect of a given drug will depend upon the technique and the measures employed. The same may be expected in other areas in which behavioral toxicity will be of concern. HERRNSTEIN and MORSE (1957), utilizing the characteristic performance on a fixed-interval reinforcement schedule as a measure of timing behavior, have demonstrated the disrupting effect of pentobarbital. WEISS, using a similar technique, has demonstrated a breakdown of timing under the influence of nalorphine. It is likely that toxic effects of a more subtle nature will be detectable either by means of more complex behavioral procedures, or by more complex analysis of simpler situations. MORSE and HERRNSTEIN (1956a) have shown that complex behavior, when measured and analyzed appropriately, will display changes in response to drug administration that are not evident upon gross inspection of the behavior. STONE, CALHOUN, and HEMMER have demonstrated that even relatively simple behavior may, upon finer analysis, be found to consist of several components that are differentially susceptible to drugs. It will remain for future clinical observation to correlate such laboratory findings with possible adaptive malfunctioning.

Emotional behavior

The possibility of drug effects upon emotional behavior is receiving considerable attention, largely as a result of the current interest in tranquilizing drugs. The problem is a difficult one, because of the poor specification of what is meant by the term, "emotional behavior". The usual course, in investigating drug-behavior relations in this area, is to employ experimental operations that contain elements analogous to those commonly supposed to be present in certain types of "emotional" situations. Such operations have typically involved the use of noxious stimuli, such as electric shocks, to generate behavior that is often labelled "anxiety"- or "fear"-type behavior.

A commonly employed technique is that of avoidance conditioning. The animals are permitted to prevent the occurrence of an electric shock by making some arbitrary response. When the avoidance response fails to occur, the animal receives a shock, which may or may not have

been preceded by a warning stimulus. As BRADY (1957) has pointed out, "few of these studies have adequately controlled for generalized motor effects, sensory decrements, and general malaise, any or all of which could produce depression of avoidance behavior independently of any specific emotional change". In illustration, WEISKRANTZ and WILSON have shown that a dose of reserpine that depressed avoidance behavior in the monkey also completely depressed behavior that was maintained by food reinforcement. Verhave, on the other hand, has shown that doses of d-desoxyephedrine that *depress* food-reinforced behavior produce an *increase* in avoidance responding.

The problem of "emotional specificity" of a drug was partially resolved by VERHAVE, OWEN and SLATER, who required their animals not only to avoid the shock but also to terminate, or escape, the shock whenever it was permitted to occur. They were then able to use this escape response as a control for nonspecific effects of the drugs. That is to say, if a drug eliminates avoidance responding but has no effect upon the escape behavior, a more satisfactory case can be made for a specific effect of the drug upon avoidance behavior. Using this technique, VERHAVE, OWEN and SLATER demonstrated that increasing doses of chlorpromazine were directly related to the magnitude of depression of shock-avoidance behavior. A lesser effect upon shock-escape behavior was observed, with doses that completely abolished all avoidance responses producing only minor decrements in the escape behavior. A similar effect was noted for morphine.

SIDMAN (1956) has demonstrated that avoidance behavior is sensitive to reserpine, with the magnitude of the effect depending not only upon the drug but also upon the behavioral variables involved in the avoidance situation. When the rats received a shock every time they permitted 20 seconds to elapse without depressing a lever, a given dose of reserpine produced no decrement in lever pressing. But when the animals received a shock only on 20 percent of the occasions when it became due because of a failure to press the lever, the same dose of reserpine produced a marked depression in the rate of avoidance responding. A finding such as this points up the necessity of investigating not only a wide range of drug doses over the total acting time of the drug, but also a wide range of the behavioral parameters that are involved in the test situation. Drug effects are dependent not only upon the nature of the chemical agent, the physiological state of the organism, and the qualitative nature of the reinforcement schedule, but also upon the quantitative properties of the contingencies maintaining the behavior in question. Further evidence of this factor has been demonstrated in the case of behavior generated by fixed-ratio reward schedules. DEWS (1956) found that methamphetamine did not appreciably alter fixed ratio behavior when 30 to 60 re-

sponses were required to produce the reinforcement. But when a ratio of 160 responses per reinforcement was used to maintain behavior, MORSE and HERRNSTEIN (1956a) observed marked alteration in both the normal baseline performance and in the behavior following administration of methamphetamine.

A different type of "emotional" situation than avoidance has also been successfully employed to evaluate tranquilizing and other types of drugs. ESTES and SKINNER pointed out that one defining aspect of emotional situations is the widespread and simultaneous alteration of large classes of behavior. Based upon this observation they introduced a method of measuring "anxiety" in terms of changes in baseline responding as a function of a stimulus that was not contingent upon the ongoing behavior. A stable level of baseline behavior was first generated by reinforcing lever pressing responses with food on a variable-interval schedule. Then while the animal was lever-pressing, a stimulus of several minutes duration was presented and terminated contiguously with the delivery of an electric shock. After several such pairings of stimulus and shock, the stimulus came to produce a complete disruption of the animal's ongoing behavior. Lever-pressing ceased during the stimulus and was resumed only after receipt of the unavoidable shock. While this conditioned suppression of ongoing behavior may or may not correspond with one's favorite definition of "anxiety", the situation in which some event signals the occurrence of a noxious, unavoidable stimulus is a common one, perhaps basic to many behavioral processes generated by aversive control (SCHOENFELD).

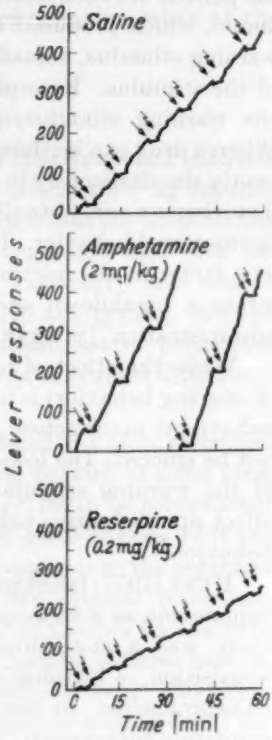

Fig. 4. Cumulative response curves showing the effect of amphetamine and reserpine on the conditioned emotional suppression. The oblique solid arrows indicate the onset of the warning stimulus, and the oblique broken arrows indicate the termination of the stimulus contiguously with the brief electric shock to the animal's feet. [From BRADY (1956a)]

Employing the conditioned suppression technique, BRADY (1956a) has demonstrated some striking behavioral changes as a consequence of amphetamine and reserpine administration. The normal disruption of ongoing behavior in the presence of a stimulus that has been paired with unavoidable shocks may be "cured" by continued reserpine treatment (Fig. 4). Amphetamine may exercise an opposite effect, intensifying the degree of behavioral suppression. Examination of Fig. 4

demonstrates that the conditioned suppression technique has a built-in control for nonspecific side effects. This control is provided by the rate of responding on the variable-interval reinforcement schedule during the periods between stimulus presentations. It may be seen that amphetamine, which produced a greater suppression of responding during the warning stimulus, actually increased the response output in the absence of the stimulus. Reserpine, while it increased the response rate during the warning stimulus, produced a lowered output between stimuli. When a drug can be shown to produce such diametrically opposite effects nearly simultaneously in a single organism, general behavioral and motor disturbances can virtually be eliminated as explanations of the changes in emotional behavior. It may be possible to invoke sensory impairment as a factor in the reserpine effect, but other data have failed to demonstrate a breakdown of discrimination as a consequence of reserpine administration [SIDMAN (1956)].

While the effect of reserpine on the emotional response (suppression of ongoing behavior) is not easily attributable to some sort of generalized behavioral malfunction, the side effect demonstrated in Fig. 4 should not be ignored. The lowered baseline rate of response during the absence of the warning stimulus suggests that reserpine may have a "toxic" effect upon adaptive behavior as well as a palliative effect upon anxiety behavior.

HUNT (1957) failed to observe any clear attenuation of the conditioned suppression as a consequence of meprobamate administration, although there was a suggestion that meprobamate may slightly retard the acquisition, or learning, of the suppression. HUNT (1956) also found that chlorpromazine, in heavy doses, does not block conditioning of the emotional suppression. Similar results were obtained in a well-controlled experiment by STEIN, working with reserpine. Even a dose of the drug that completely abolished all lever-pressing behavior failed to interfere with the acquisition of the conditioned suppression, tested after the drug had worn off.

HILL, BELLEVILLE and WIKLER (1954a) have found striking effects of morphine upon the conditioned suppression in rats. They report an increasing attenuation of the emotional suppression with increasing doses of morphine sulfate [HILL et al. (1954b)]. These writers interpret their data as an indication that "one of the major actions of a potent analgesic is the reduction of behavior-disrupting anticipatory response to noxious stimuli" [HILL et al. (1954b)]. It is possible, however, that the alleviation of the conditioned suppression is only incidental to the analgesic effect. If the shock is made less painful, it is likely that the anticipatory disruption of behavior will disappear through the normal extinction process BRADY (1955). More conclusive support for the attrac-

tive hypothesis that analgesic agents exercise at least part of their effect through anxiety reduction may be obtained by employing a non-painful aversive stimulus instead of electric shock, e.g., LINDSLEY and JETTER, MORSE and HERRNSTEIN (1956b). This would permit a test of the effect of morphine upon the anticipatory disruption of behavior, while at the same time ruling out the analgesic effect.

Drug-behavior interactions

Recent research has made it abundantly clear that drugs and behavior are, in a wide sense, interactive. The behavioral effect of a drug depends qualitatively and quantitatively upon the variables that are maintaining the behavior at the time. SIDMAN (1956) has suggested that such dependence may be responsible for the notorious variability that almost inevitably hampers the clinical evaluation of a CNS-acting drug. MILLER has also demonstrated that even under a constant set of behavioral variables, various aspects of a given type of behavior may react differently to a drug.

But drug-behavior interactions may be considered in a more restricted sense. If a drug alters the frequency or temporal pattern of some form of behavior, it is possible that the new pattern may, itself, be perpetuated after the drug has been withdrawn. This might occur especially if the drug-induced change in behavior were more advantageous to the organism than the previous mode of behavior. While the original conditions maintaining the behavior may have been such as to hamper an adaptive adjustment, the drug, by reducing the degree of control of these factors, may permit the organism to learn a more adaptive response. An effect such as this is probably the one most to be sought in testing drugs for efficacy in the treatment of behavior disorders.

Unfortunately, there has been almost a complete lack of experimental attention to this type of drug-behavior interaction. Relevant observations have, for the most part, been secondary ones in experiments directed at other problems. In one of the few direct attacks upon the problem, HUNT (1956) checked the effect of chlorpromazine upon the extinction of a conditioned emotional response. Suppression of ongoing behavior was first established by pairing a stimulus with shock until the ongoing behavior was completely disrupted during the anticipatory signal. Extinction was then carried out, with and without the drug, by presenting the warning signal but omitting the shock. HUNT found that animals which were drugged during the extinction procedure still displayed the anticipatory behavioral disruption after the drug was discontinued. In animals which were not drugged, the extinction procedure had its usual effect of eliminating the emotional response. Thus chlor-

promazine, far from permitting the animals to unlearn their fear, actually prevented the normal extinction process from occurring.

SIDMAN (1956) has investigated the permanence of a reserpine effect upon avoidance behavior. PÖREN and SIDMAN had demonstrated that even when 80 percent of the shocks normally received by the animal for failure to make the avoidance response were withheld, the rate of avoidance behavior did not diminish. Under the influence of reserpine, however, the rate of avoidance responding fell to a more appropriate level on this intermittent shock procedure [SIDMAN (1956)]. But when the drug was discontinued, avoidance responding returned to the unnecessarily high level that had prevailed prior to "treatment". Again, then, we observe the failure of an adaptive behavioral effect to perpetuate itself after the drug was withdrawn.

MORSE and HERRNSTEIN (1956a) demonstrated an effect that may be classified as at least partially successful in revealing a continued behavioral change following administration of a drug. Using a fixed-ratio reinforcement procedure, they required 160 responses before a food reinforcement could be procured. With such a large ratio of responses to reinforcements, the behavior typically was characterized by high rates alternating with long pauses during which no responses were emitted. The pauses were almost completely eliminated by a large dose of methamphetamine, so that a great many more food reinforcements were obtained under the drug. On the following day, 23 hours after the drug had been administered, there was a clear residual effect of the drug, with higher response rates, few pauses, and more frequent reinforcements. Eventually, however, the behavior returned to its normal "strained" state, indicating that the residual effect of the drug was not permanent.

Drugs, behavior, and the nervous system

With the advent of more precise methods for generating and measuring behavior, there has developed an increasing experimental interest in the relations between behavior and other biological processes. By means of central nervous system lesions, electrical stimulation and recording, and biochemical assay techniques, knowledge of the relations between behavior and the internal functioning of living organisms is steadily increasing in scope. Drugs, too, promise to add to the understanding of both behavior and the nervous system. A relatively sophisticated area of research, barely initiated as yet, is the investigation not simply of the effects of drugs upon behavior, or upon the nervous system, but of the effects of drug activity upon known *relations between* behavior and the nervous system.

An experiment that is likely to become a classic prototype in this area is that of MASON and BRADY. It had first been determined that the conditioned emotional suppression was accompanied by significant elevations of plasma 17-hydroxycorticosteroid levels (MASON et al.). Other experiments demonstrated that reserpine markedly attenuates the conditioned emotional suppression of ongoing behavior [BRADY (1956b)]. The next step was to examine the relation between reserpine activity and the adrenal-cortical response to emotional conditioning. MASON and BRADY found that when the behavioral suppression had been abolished by reserpine, the corticosteroid elevation also failed to appear during the "anxiety" stimulus. When the drug treatments were discontinued, the behavioral suppression reappeared and corticosteroid elevations were again recorded. Although the behavioral and endocrine responses thus appeared to be intimately related, as was suggested by their correlated changes, the recovery of the behavioral suppression and the corticosteroid response did not follow precisely the same time course after the drug had been withdrawn. The steroid response returned to normal well after the conditioned suppression had reappeared. The writers suggest that this difference in recovery time may indicate at least partially independent neural mechanisms underlying the two responses.

Research such as this, in which information concerning drug action is obtained and, *in addition*, the drug effect is utilized to clarify relations between behavior and physiology, has been rare. In most of the experiments of this sort that are reported, the physiological variables involved have been those that *produce*, rather than *accompany*, behavioral effects. A major problem in these experiments is the lack of precise information, behavioral or otherwise, concerning the effects of the physiological operations involved. One such operation consists of experimental lesions of the central nervous system. WEISKRANTZ and WILSON, testing the action of reserpine upon normal and amygdaloidectomized monkeys in an avoidance situation, found that the lesions did not interfere with the depressant effect of a large dose of the drug. HUNT and BECKWITH utilized phenurone, dilantin, and amphetamine to investigate the effects of electro-convulsive shock (ECS) upon the conditioned emotional suppression. It had previously been shown that electro-convulsive therapy attenuated the emotional suppression (BRADY and HUNT). HUNT and BECKWITH found that when the drugs were given intercurrently with ECS, phenurone blocked the attenuating effect of ECS while dilantin or amphetamine increased the attenuating effect. OLDS, KILLAM and BACH-Y-RITA have presented data in yet another area, investigating the effects of drugs upon behavior that is involved in electrical self-stimulation of the brain.

Their technique made use of the finding, by OLDS and MILNER, that when rats are permitted to press a lever and thereby electrically stimulate specific brain structures, such stimulation acts as a reinforcement. That is, the animals press the lever at a high rate. OLDS, KILLAM and BACH-Y-RITA designed their experiment to determine whether different drugs would affect self-stimulation rates for some electrode loci more than for others. They found that reserpine depressed the response rate markedly in animals that were stimulated in the hypothalamus or in the amygdala, but produced only a minor depression when the electrodes were located in the septal region. Chlorpromazine produced similar effects, while pentobarbital did not show selective effects among the stimulated areas. Although the close temporal spacing of drug administrations somewhat clouds the data of these experiments, particularly in the case of reserpine, whose long-term effects are well-known, the technique will undoubtedly yield basic information concerning both drug action and behavior-nervous system interrelations. There have been, finally, a few experiments in which the chief interest has been in the influence of chemical agents upon the efficacy of specific motivating operations, e.g., deprivation of food, oxygen, or heat. MILLER found that amphetamine decreased the amount of food consumption by hungry rats, and lowered the concentration of quinine, mixed with milk, that the animals would accept. The rate of lever-pressing, reinforced on a variable-interval schedule, declined with higher doses of amphetamine and increased with lower doses. The rate increase was consistent with earlier reports by SKINNER and HERON and WENTINK. WEISS and DANFORD utilized an ingenious technique whereby rats subjected to cold temperatures were reinforced for lever-pressing by the activation of an infrared heat lamp. They found that animals which were severely deprived of both food and pantothenic acid markedly increased the rate of lever pressing for the heat reward. BERRYMAN, MECHNER, KELLER and METLAY employed behavioral techniques to assess possible interactions between anoxia and tocopherol. They found that anoxia produced an early and abrupt interruption of behavior maintained by food reinforcement, and a slow, gradual depression of avoidance behavior. Tocopherol appeared to have some tendency to postpone the behavioral effects of anoxia, the drug effect being most pronounced on avoidance behavior.

Human behavior

This has been a review of experimental data on drug-behavior relationships obtained largely by means of operant conditioning techniques with animal subjects. It will be noted that the vast majority of the references were published after 1950. The validity of extrapolations to the human sphere remains an empirical problem which will require a

considerably longer period of time to evaluate. There are, however, encouraging signs. Operant methods have been successfully employed with mice, rats, guinea pigs, pigeons, cats, dogs, monkeys, chimpanzees, and both normal and psychotic human children and adults. The behavioral principles based on this work appear to possess great species generality, and even in those cases where the behavior differs from one species to the next, the control techniques themselves remain generally applicable. To the extent that the behavioral principles are applicable to humans, we may have confidence in the applicability of data on drug-behavior relationships also. A major obstacle in the way of determining the valitity of extrapolations from the animal laboratory to the clinic is the lack of precise and reliable methods for evaluating human behavior problems. BRADY (1956) has provided a succinct statement of the problem: "It seems reasonable, for the present, to define differential behavioral properties of various pharmacologic agents at any level where experimental controls permit operational analysis, allowing empirical relationships to take form as refinements in clinical methods provide reliable comparative information."

A promising beginning has been made in the direction of refining clinical observations through the use of operant conditioning techniques with psychotic patients. An outline of the methodology has been presented by SKINNER, SOLOMON and LINDSLEY (1954). Although some data have been reported on the effects of chlorpromazine and lysergic acid, adequate control data are not yet available [SKINNER et al. (1956)]. While other laboratories have also begun to extend the techniques to human subjects, there have as yet been no published reports on the effects of pharmacologic agents.

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Relationships of Psychotomimetic to Anti-Serotonin Potencies of Congeners of Lysergic Acid Diethylamide (LSD-25)

By

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It has been postulated that LSD induces a psychosis by creating a relative deficiency of serotonin within the brain (GADDUM 1953; WOOLEY and SHAW 1954a). The converse hypothesis—that LSD creates a psychosis by acting like serotonin in brain—has also been formulated (WOOLEY and SHAW 1954b; RINALDI et al. 1956). Evidence for and against both hypotheses has recently been reviewed (PAGE 1958). Serious doubt of the validity of the deficiency hypothesis was created by the finding that D-2-Brom-diethylamide of lysergic acid (BOL-148), which is as potent or more potent than LSD in blocking serotonin in isolated smooth muscle preparations, was not a psychotomimetic drug (CERLETTI and ROTHLIN 1955; ROTHLIN 1957), or only a very weak one (SCHNECKLOTH et. al. 1957). Availability of a number of congeners of LSD-25 with varying potencies as antagonists of serotonin on isolated uterine muscle of the rat made possible a more detailed examination of the relationship of potency of drugs of this type as serotonin antagonists to potency as psychotomimetics. In addition, availability of these compounds provided an opportunity to study the relationship of chemical alterations in the LSD molecule to psychotomimetic effect.

Methods

Drugs. The congeners of LSD studied[1] are listed in Table 2, which also shows the code designations of the various substances. Fresh solutions of all drugs in distilled water were given orally to patients in a fasting state. Doses were calculated on the basis of body weight (micrograms per kilogram) and were expressed as the weight of the salts. Subjects were always unaware of the identity of the drugs (though they expected that they would experience LSD-like effects) and, when detailed comparisons were made, neither the subjects nor the observers knew the nature of the drugs under study ("double-blind" procedure).

[1] These drugs were made available through the courtesy of Dr. R. BIRCHER, Sandoz Pharmaceuticals, Hanover, N. J. The code designations are those of the Sandoz Company.

Subjects. The persons who served as subjects were all Negro male prisoners whe were serving sentences for violation of the narcotic laws, and whoe volunteered for the experiments. All were healthy physically and presented no symptoms suggestive of psychotic disorder. All patients had received LSD prior to entering on these experiments and were familiar with the subjective effects induced by that drug. Because of the large numbers of drugs studied and the long length of time over which the investigations were carried out the same group of subjects did not receive all the drugs. For this reason, estimates of the comparative potencies of the various drugs are affected by possible variation between groups, and can be considered only as approximations.

General Conditions. Experiments were conducted in a special ward devoted to clinical research. Patients entered the ward on the afternoon prior to the experimental day and remained until all drug effects had subsided. They were housed in individual rooms, but were allowed to leave them and to mix with other patients in a common dayroom if they so desired. Experiments were done at weekly intervals in order to prevent the development of tolerance.

Observations. The following observations were made, by methods previously described (ISBELL, et al. 1956), at hourly intervals, twice before and eight times after administration of the drugs: threshold for the kneejerk, systolic blood pressure after resting in bed for ten minutes, and pupillary diameter. Beginning thirty minutes before the drug was given, a modification[1] of the questionnaire of ABRAMSON et al. (1955) was administered hourly, once before, and eight times after the drug was given. Short mental status examinations were performed after the questionnaires had been completed and "clinical grades" of the LSD reaction assigned on a scale of 0—4 according to the system described by ISBELL[2] et al. (1956).

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[1] The questionnaire consists of 57 questions covering various symptoms frequently reported after LSD-25. Typical questions are: Are you nervous? Do you feel strange? Does any part of your body feel different? Have you seen any colored lights with your eyes closed? Do the lights form any pictures that you can name? Is someone controlling your mind?

The questionnaire has several disadvantages: It may suggest symptoms; few positive responses are given to many questions; and it does not cover all the mental phenomena reported after LSD.

The questionnaire has the advantages that a systematic record is obtained and the number of positive responses is highly correlated with the dose of LSD.

[2] The grades are assigned on the basis of the presence of the following symtoms:

Grade 0: Absence of any reaction,

Grade 1: Anxiety and nervousness without perceptual distortion or hallucinations,

Grade 2: Anxiety, nervousness and perceptual distortion but without "true" hallucinations,

Experiments. Since most of the drugs had not previously been studied in man, it was necessary to carry out preliminary experiments to determine the dosage which would induce a reaction roughly equal to that produced by 1.0 mcg/kg of LSD. Such preliminary experiments were not "double-blind" since the observers were, for reasons of safety, aware of the drug and the dose. In this phase of the study placebos were not used. The dosage in the first trial of a new drug in the preliminary phase was always 0.5 mcg/kg. If no effect was observed, the dose was doubled in the next experiment with a different subject and the procedure repeated until LSD-like effects began to be observed, or until a dose of at least 50 mcg/kg had been reached without evidence of any psychotomimetic action. The number of subjects used in preliminary trials varied from 5, in the case of ALD-52, to 58, in the case of LAE-32. No psychotomimetic effects were observed with L-LSD (maximum dose 70 mcg/kg), I-LSD (50 mcg/kg), and MBL-61 (175 mcg/kg), so that further comparisons of these drugs with LSD were not undertaken.

After the preliminary experiments were completed, the drugs which has psychotomimetic properties were compared with LSD in more detail. The observations and general methods were those described above. Six groups of subjects were used. Each group received a placebo, LSD, and one to three of the new drugs. Order of administration of the various compounds and of the various doses was randomized and the "double-blind" procedure followed throughout, with identity of the drugs and the doses used being unknown to both subjects and observers. The six groups of patients, the number of patients in each group, and the doses of the drugs are shown in Table 2.

Analysis of Data. The areas under the time-action curve over the eight-hour period after administration of drugs was calculated by the method of WINTER and FLATAKER (1950), as described elsewhere (ISBELL et al. in press) in the cases of threshold for the kneejerk, systolic blood pressure and pupillary diameter. The positive responses on the questionnaire were counted over the entire eight hour period, eliminating answers which were also scored positively prior to drug administration. The highest "clinical grade" observed was used in tabulating the results, regardless of the time at which it occurred. Means and standard errors of means were calculated according to standard techniques. In

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Grade 3: Anxiety, nervousness, and "true hallucinations" (an hallucinatory experience which the patient can definitely name as an object or a sound as contrasted with perception of lights, meaningless patterns or simple hyperacusis). In this grade, insight is maintained (patients state that effects are due to the drug).

Grade 4: Same as Grade 3 with insight lost (patient does not realize that effects are due to the drug).

Table 1. *Comparison of psychotomimetic and antiserotonin potencies*

Code	Compound	Dose approximately* equivalent to 1.0 mcg/kg of LSD-25	Relative psychotomimetic activity (LSD-25 = 100)	Relative** antiserotonin activity (LSD-25 = 100)	Remarks
		A. Stereoisomers			
LSD-25	d-Lysergic acid diethylamide	1.0	100	100	
L-LSD	l-Lysergic acid diethylamide	>70	0	0	No psychotomimetic effect in doses used
I-LSD	d-Iso-lysergic acid diethylamide	>50	0	0	No psychotomimetic effect in doses used
		B. Variations in amide group			
DAM-57	d-Lysergic acid dimethylamide	10	10	23	Effect similar to LSD, onset quicker and course shorter
LAE-32	d-Lysergic acid monoethylamide	20	5	12	Effect similar to LSD; course shorter
LPD-824	d-Lysergic acid pyrrolidide	10	10	5	Effect similar to LSD; course shorter
LSM-775	d-Lysergic acid morpholide	9	11	2	Effect similar to LSD; course shorter
		C. Substitutions in ring system			
MLD-41	d-1-Methyl lysergic acid diethylamide	3	33	370	Effect similar to LSD; onset slower
ALD-52	d-1-Acetyl lysergic acid diethylamide	1	100	210	Effect similar to LSD; course similar
BOL-148	d-2-Brom-lysergic acid diethylamide	>86	<2	103	Only partial LSD effect; course shorter
MBL-61	d-1-Methyl-2-brom-lysergic acid diethylamide	>175	<1	533	No spychotomimetic effect in doses used
		D. Substitutions in rings and variations in amide			
MLA-74	d-1-Methyl-lysergic acid monoethylamide	25	4	835	LSD-like; short course
ALA-10	d-1-Acetyl-lysergic acid monoethylamide	15	7	39	LSD-like; short course
MPD-75	d-1-Methyl-lysergic acid pyrrolidide	>20	<5	130	Only partial LSD effect; short course

* See text for method of estimation.

** Taken from data of CERLETTI and DOEPFNER.

Table 2. *Comparative effects of congeners of LSD*

Drug	No. pts.	Dose mcg/kg	Patellar* reflex	Blood* pressure	Pupillary* size	Number of positive answers	Grade
Placebo	9		0.9 ±1.2	50.7±18	−1.8 ±1.1	0 ± 0	0 ± 0
Placebo	8		0.4 ±1.7	29 ±25	4.3 ±1.8	0 ± 0	0 ± 0
LSD-25	9	0.75	5.7 ±1.6	80 ±20	15.8 ±2.4	10 ± 4	0.2 ±0.2
LSD-25	9	1.5	8.7 ±1.2	94 ±15	18 ±2.3	53 ±21	2.4 ±0.4
LPD-824	9	7.5	0.6 ±1.3	50 ±16	9.4 ±1.5	7 ± 3	0.4 ±0.2
LPD-824	9	15.0	2.2 ±0.95	55 ±14	6.6 ±1.4	19 ± 7	1.1 ±0.1
DAM-57	9	7.5	5.1 ±0.8	76 ±15	19.7 ±7	26 ± 9	1.8 ±4
DAM-57	9	15.0	5.1 ±1.6	105 ±23	13.3 ±2.2	51 ± 6	2.9 ±1
LSM-775	9	4.5	2.5 ±1.1	68 ±18	6.3 ±2.2	7 ± 4	0.55±0.2
LSM-775	9	9.0	1.4 ±1.5	65 ±13	9.4 ±2.5	16 ± 8	0.8 ±3
Placebo	10		1.5 ±0.8	36 ± 6	3.8 ±1.6	1.0± 3	0 ±0
LSD	10	1.0	9.6 ±1.3	98.5±14	17.7 ±1.3	36 ±13	1.0 ±0.35
LSD	8	2.0	10.4 ±1.3	106 ± 6	19.3 ±1.9	48 ±15	1.8 ±0.37
MLD-41	6	3.0	12.3 ±1.4	114 ±15	18.2 ±2.6	19 ±22	1.0 ±0.55
MLD-41	10	4.0	12.4 ±1.1	115 ±16	17.2 ±1.8	34 ±19	1.3 ±0.3
MLD-41	6	6.0	11.4 ±2.0	127 ±20	18.5 ±2.0	42 ±13	2.0 ±0.3
Placebo	6	—	3.0 ±1.3	38 ±14	3.3 ±1.2	5 ± 5	0 ±0
LSD	6	1.0	9.2 ±2.0	93 ±14	17.4 ±1.9	50 ± 7	1.5 ±4
LSD	4	1.5	9.8 ±2.8	87 ±38	16.8 ±1.6	21 ± 9	1.0 ±7
ALD-52	6	1.0	10.7 ±1.8	115 ±11	17.2 ±2.2	54 ±11	2.0 ±0.4
ALS-52	4	1.5	13.0 ±2.4	137 ±25	17.0 ±3.2	53 ±18	2.5 ±0.7
Placebo	8		2.8 ±5.2	49 ±19	3.0 ±0.8	0 ± 0	0 ±0
LSD-25	8	1,5	10.7 ±1.8	142 ±19	15.7 ±4.5	86 ±18	2.1 ±0.3
MLA-74	8	25	4.7 ±1.9	77 ±20	9.0 ±2.6	22 ± 6	0.9 ±0.3
ALA-10	8	15	3.0 ±1	88 ±26	3.5 ±1.5	30 ±10	1.1 ±0.47
Placebo	8		1.9 ±0.9	27 ±18	0.7 ±2.3	0 ± 0	0 ±0
LSD-25	8	1.5	9.8 ±1.5	96 ±15	15.9 ±1.1	58 ±12	1.8 ±0.1
MPD-75	8	20	0.16±0.5	57 ±14	4.2 ±1.6	11 ± 3	0.4 ±0.2
LAE-32	8	20	0.8 ±0.7	42 ±12	6.7 ±1.2	2.6± 9	1.0 ±0.16
Placebo	15		0.75±0.6	27.2± 8	−0.48±0.7	2 ± 1.2	0 ±0
LSD-25	15	0.5—1.5	9.2 ±1.3	108 ±16	15.7 ±1.4	61 ±11	2.0 ±0.3
BOL-148	15	75—110	2.52±0.8	38 ±12	6.1 ±1.3	13 ±47	0.6 ±0.15

* Figures given are mean ± standard errors of areas under time-action curves and are expressed as "millimeter-hours" (blood pressure, pupils) and "degree-hours" (kneejerk). The double horizontal lines indicate the six groups of patients used in assessing psychotomimetic potency. All patients within a group received all the drugs in all the doses listed in that group.

the case of BOL-148, data for doses ranging from 75—110 mcg/kg were combined and compared with data for various doses of LSD-25 (0.5—1.5 mcg/kg).

The approximately equivalent psychotomimetic doses shown in Table 1 were chosen by inspecting the data on number of positive answers and clinical grade in Table 2, and selecting the dose of the new drug which most nearly approximated the effect seen or expected from 1.0 mcg/kg of LSD. Though the method is inexact, it is felt that

the dosages assessed in this way reflect the relative psychotomimetic potencies of the new drugs with sufficient accuracy to permit meaningful comparisons of potencies as psychotomimetics with potencies in antagonizing serotonin.

The data for each measurement made on each dose of each drug were tabulated and averaged for each hour before and after administration of the compound. These data on time-action of the various drugs are too voluminous to publish *in toto*, but the time courses as reflected by the average number of positive responses on the questionnaire after the largest doses of the drugs that had definite psychotomimetic effects is shown in Table 3.

Table 3. *Time course after highest dose of various drugs as reflected by average number of positive responses on the questionnaire*

Drug	Dose mcg/kg	Number of subjects	Hours before or after drug								
			−½	+½	+1½	+2½	+3½	+4½	+5½	+6½	+7½
Placebo	—	9	0	0.7	0.2	0	0	0	0	0	0
LSD-25	1.5	9	0	6.9	8.6	10.1	11.0	9.6	2.2	4.2	0.7
DAM-57	15	9	0	19.7	13.6	9.3	4.0	2.6	1.0	0.7	0
LAE-32	20	8	0	12	8	4	1.5	0.3	0	0	0
LPD-824	15	9	0	4.7	6.4	3.8	2.4	1.3	0.4	0.2	0
LSM-775	9	9	0	7.5	5.0	2.6	0.6	0.1	0.1	0	0
MLD-41	6	6	0	2	12	14	8	5	1	0	0
ALD-52	1.5	4	0	7.5	9.0	11.0	8.5	7.0	6.0	4.0	0
BOL-148	86*	15	0	5	3	2	2	1	0	0	0
MLA-74	25	8	0	9	5	4	2.2	0.8	0.3	0	0
ALA-10	15	8	0	16	8	7	4.5	1	0.3	0	0
MPD-75	20	8	0	28	3.8	2.6	0.9	0.3	0.1	0	0

* Average dose (range 75—110 mcg/kg).

Results

The combined data are presented in Table 2, and the approximations of equivalent psychotomimetic doses are compared with the potencies as serotonin antagonists in Table 1. Data on serotonin antagonism were taken from the paper of CERLETTI and DOEPFNER (1958). The only alteration in the LSD molecule which did not reduce psychotomimetic potency was substitution of an acetyl group on the indole nitrogen (ALD-52). All other alterations resulted in diminished activity. Inactivation was greatest in the case of the two compounds, BOL-148 and MBL-61, in which a bromine atom replaced a hydrogen at position two of the indole ring. Alterations in the amide group all reduced activity and shortened the time course. The stereoisomers of LSD did not possess any significant psychotomimetic potency.

In general, the changes in the patellar reflex, blood pressure, and pupillary size parallelled the "mental" effects (questions and grade).

The greatest deviations from such parallelism occurred with the compounds with short-lengths of action (on the kneejerk, in the case of MLA-74, ALA-10, MPD-75 and LAE-32; and on pupillary diameter, in the case of ALA-10). This lack of parallelism in these cases is partly an artefact of the method of analysis. The means for effects on the patellar reflex, pupillary size, and blood pressure are computed over a period of eight hours. The length of action of these four drugs is four hours or less. Therefore, the total degree of change over the entire eight-hour period of observation is less than is the case with LSD, which has effects persisting for at least eight hours.

Discussion

There are very few reports in the literature concerning the effects of these congeners of LSD in man. SOLMS (1953, 1956) found that 0.5 to 0.75 mg (total dose) subcutaneously of LAE-32 induced a psychosis characterized by pseudo-hallucinations and illusions. In smaller doses, an apathetic, adynamic state was often seen. In our experiments, the apathy described by SOLMS was never observed, and the dose of LAE-32 approximately equal to 1 mcg/kg of LSD was 20 mcg/kg, a total dose 1.4 mg for a 70 kg man. These differences in our experiments and those of SOLMS may be due in part to the different routes of administration. JARVIK et al. (1955) also found that LAE-32 was much less active than LSD as a psychotomimetic. Geronimus et al. (1956) reported that L-LSD induced no psychotomimetic effect in a dose (total) of 100 mcg orally. MURPHREE et al. (1958) reported that L-LSD was inert in does of 4 mg. Our data on L-LSD agree with both these groups of authors. I-LSD has not been previously studied. MURPHREE et al. state that 800 mcg of LPD-824 had a fleeting effect equal to about one-tenth as much LSD. Our data confirms this estimate. GOGERTY and DILLE (1957) found that 75 mcg (total dose) of LSM-775 induced short-lasting effects in 2 subjects, which seemed equivalent to those following 50 mcg of LSD. In contrast, we found LSM-775 to be approximately one-tenth as active as LSD. ROTHLIN (1957) states that DAM-57 did not induce any psychic changes but did cause autonomic disturbances in man. In our experiments, DAM-57 was one-tenth as active as LSD, and induced both psychic and autonomic changes when given in this dose. Our data confirm ROTHLIN's statement that ALD-52 is as active a psychotomimetic as is LSD. ABRAMSON et al. (1958) reported that MLD-41 is approximately one-third as potent as LSD as a psychotomimetic, which agrees with our estimate.

BOL-148 deserves special comment. CERLETTI and ROTHLIN (1955), and ROTHLIN (1957) state that BOL-148 did not have psychotomimetic effect in doses 20 times as great as the psychotomimetic dose of LSD.

JARVIK et al. (1955), likewise, reported little effect from 5 to 7 mcg/kg of BOL. SNOW et al. (1955) observed no mental symptoms in patients with malignant carcinoid who had received as much as 7.5 mg of BOL. SCHNECKLOTH et al. (1957), however, noted LSD-like mental effects after intravenous infusion of 18 to 22 mcg/kg of BOL. In our experiments, BOL did not have any psychotomimetic effects in doses less than 50 mcg/kg. However, doses greater than 70 mcg/kg did consistently induce mild mental changes, although a complete spectrum of LSD-like effects was never observed.

The data show that a high degree of activity as a serotonin antagonist in isolated smooth muscle preparations is not necessarily correlated with high psychotomimetic potency. Thus MBL-61 had no psychotomimetic effect in doses of 175 mcg/kg even though it is five times as potent as LSD as a serotonin blocker on the isolated uterine muscles of the rat uterus. Other dissociations between potency as serotonin antagonists and potency in inducing psychoses are apparent in the cases of MLD-41, BOL-148, MLA-74, and MPD-75. There is, however, no example of low potency as a serotonin antagonist being associated with high potency as a psychotomimetic. The data, therefore, do not support the hypothesis that LSD (and similar drugs) causes a psychosis by competing with serotonin within the central nervous system, but do not disprove it.

Summary

1. The psychotomimetic potency of 13 congeners of LSD-25 has been approximately determined in man.

2. With the exception of acetylation of the indole nitrogen, all the changes made in the LSD molecule reduced psychotomimetic potency. Bromination at carbon 2 caused the greatest inactivation.

3. High potency as a serotonin antagonist in isolated smooth muscle preparations was not correlated with high potency as a psychotomimetic.

4. The data do not support but do not disprove the "serotonin deficiency" hypothesis of the LSD psychosis.

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Comparison of the Reactions Induced by Psilocybin and LSD-25 in Man

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With 1 Figure in the Text

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The use of certain intoxicating mushrooms by Indians in Mexico has been reviewed by HOFMANN et al. (1958). V. P. and R. G. WASSON (1957) have reported the way in which the mushrooms are taken by the Mexican Indians and the hallucinatory experiences occurring following their ingestion. HOFMANN et al. (1958a) have described the identification of the mushrooms and their successful culture by HEIM, and by HEIM and CAILLEUX. HOFMANN et al. (1958) isolated a pure compound from the mushrooms which had the characteristics of an indoleamine and which contained phosphorus. Later the compound was identified as 0-Phosphoryl-4-hydroxy-N-dimethyl tryptamine, was synthesized (HOFMANN 1958; HOFMANN et al. 1958a and b) and named psilocybin. Preliminary studies in man (HOFMANN et al. 1958a) showed that the compound, in doses of 4 to 8 mg, induced an abnormal mental state resembling that seen after LSD or mescaline. In animals (CERLETTI 1958), psilocybin caused neurovegetative symptoms although it had no high degree of activity on peripheral autonomic structures. The autonomic effects of psilocybin seemed to be due to central sympathetic stimulation. It facilitated spinal reflexes and caused an "arousal" pattern in the EEG, although motor behavior was depressed.

Because of the chemical relationship of psilocybin to serotonin and to bufotenine, and because of the possible role of serotonin (5-hydroxytryptamine) in the function of the central nervous system, a detailed comparison of the effects of psilocybin with those of the diethylamide of d-lysergic acid (LSD-25) in man was thought to be of interest.

Methods

Preliminary Experiments. In order to confirm the dose range reported by HOFMANN et al. (1958a), several preliminary experiments were done in which 7 volunteers ingested psilocybin orally in doses ranging from 0.5 to 8.0 mg/70 kg of body weight. These experiments indicated that psilocybin caused definite mental effects in doses of 2 to 8 mg/70 kg which were accompanied by pupillary dilatation, increased tendon reflexes,

and increased blood pressure. The mental effects of psilocybin seemed to resemble those of LSD. A more detailed experiment was the carried out utilizing 9 patients.

Subjects. The subjects used in these experiments were all negro males who were former drug addicts and who were serving for violation of the United States narcotic laws. Their ages ranged between 22 and 40 years. All were in good physical health, and none presented evidence of any of the major psychoses. All had experienced the effects of LDS-25 in previous experiments.

General conditions. The experiments were all conducted in a special ward devoted to clinical research. Observations were made by specially trained attendants with many years of experience in observing patients who have received various drugs. The patients entered this special ward on the night before the experiments were conducted. They were awakened at 6:30 a.m. Each patient was free to mix and mingle with other patients in a common dayroom, or to remain in his own room, as he preferred.

Drugs. LSD-25 and psylocybin[1] were administered in solution in raspberry syrup. The syrup was used in order to mask the slightly bitter taste of psilocybin. Drugs were administered at 8 a.m. with the patients fasting. All patients received, in a randomized balanced order, a placebo, 1.0 and 1.5 mcg/kg of LSD, 57, 86, and 114 mcg/kg of psilocybin (4.0, 6.0 and 8.0 mg/70 kg). The "single-blind" procedure was followed throughout. The patients were not aware of the identity of the drugs given on a specific day but one of the attendants, for reasons of safety, did know what medication had been given.

Observations. The following observations were made at hourly intervals from 7 a.m. to 4 p.m. after the patients had rested quietly for ten minutes in bed: rectal temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure, diameter of pupils, and thresholds for eliciting the kneejerk. Methods for making these measurements were those previously described (ISBELL et al. 1956; ISBELL et al. 1958). At hourly intervals from 7:30 a.m. to 3:30 p.m. patients completed a questionnaire[2] modified from that of ABRAMSON et al. (1955), with the

[1] We are indebted to Drs. R. BIRCHER and C. HENZE of the Medical Department, Sandoz Pharmaceuticals, Hanover, New Jersey, for generous supplies of LSD-25 and psilocybin.

[2] The questionnaire consists of 57 questions and includes such items as: Are you nervous? Are you confused? Are you having difficulty in thinking? Have you had any peculiar experiences? Do things appear large or small? Is someone controlling your mind, etc.? The questionnaire has several disadvantages: It may suggest symptoms; it does not cover all the mental phenomena observed after LSD, and might not cover phenomena experienced after a different drug. It has the advantage that a systematic record of certain symptoms is obtained at definite intervals before and after administration of the drug. The data obtained in the same group of subjects are reproducible and good dose-effect responses are obtained after different doses of LSD.

help of an aide. A short mental status examination was made one and one-half to two hours after the drug and a grade[1] (scale 0-4) of the intensity of the reaction was assigned according to the system used in rating the intensity of the LSD reaction (ISBELL et al. 1956).

Analysis of data. The change after drugs in rectal temperature, pulse and respiratory rates, systolic and diastolic blood pressures, puillary size, and threshold for elicitation of the kneejerk were calculated by subtracting the figures obtained at various hours after the drugs from the average of the two pre-drug observations. The areas under the time-action curves for each subject, and for each dose of each medication for the various measurements, were then calculated by the method of WINTER and FLATAKER (1950). This procedure converts all the data on a particular measurement for an individual receiving a given dose of a drug to one figure. The number of positive responses on the questionnaires after the drugs were counted over the entire observation period, eliminating answers which were also scored positively before the drugs. Means and standard errors of means were calculated according to standard statistical techniques. The *t*-test for paired observations was used in evaluating the significance of differences in the "objective" (temperature, pupils, etc.) signs (EDWARDS 1946). Nonparametric tests (WILCOXON 1949) were used in evaluating the significance of differences in the number of positive responses on the questionnaire and on the clinical grade.

Measurements of pupillary diameter (an "objective" measure) and number of positive responses on the questionnaire (a "subjective" measure) were tabulated and averaged at each observation time before and after the drugs, in order to obtain time-action curves.

Regression lines for dose-effect curves, calculations of relative potency and confidence limits were calculated by the methods described by BLISS (1952).

In order to compare the pattern of subjective response, the 57 questions constituting the questionnaire were classified into nine cate-

[1] The clinical grade was based on the mental status examination and grades assigned according to the following scheme: Grade 0: No reaction, Grade 1: Anxiety and nervousness without perceptual distortion or hallucinations, Grade 2: Anxiety, nervousness and visual perceptual distortion without "true" hallucinations, Grade 3: Anxiety, nervousness, perceptual distortion and "true" hallucinations but with insight maintained (patients report that effects are due to drugs), and Grade 4: Same as grade 3, except that insight (realization that the effects are due to the drug) is lost.

The grading system has the disadvantage that the various grades may not form a continuous scale. It gives no information concerning the quantitative aspects of the symptoms which go into determining the grades. Like the questionnaire, however, it yields reproducible data on repeated administration of the same dose of LSD, and good dose-effect responses are obtained.

gories[1]. The questionnaires were then scored by counting the number of patients responding positively to a given question two or more times after administration of the drug, after which the number of patients responding positively to a given category of questions was determined by adding the totals for all the questions constituting the particular category.

Results

General clinical description of the psilocybin reaction. This description of the reaction occurring after psilocybin is based primarily on the data obtained with the 114 mcgm/kg dose. Following administration of psilocybin orally the patients usually spontaneously reported the first subjective effects within 10 to 15 minutes. These effects consisted of vague sensations that things looked, felt, or seemed peculiar, and were accompanied by mild anxiety. After 30 minutes, anxiety became quite definite and was expressed as consisting of fear that something evil was going to happen, fear of insanity, or of death. At this time, changes in mood, usually in the direction of elation (despite the anxiety) and sometimes in the direction of depression, occurred. The patients reported increased keenness of hearing, paresthesia, and blurring of vision. One hour after the drug the reaction was well developed. Anxiety became more marked and, in some cases was intense. Elation, when present, was great and in some patients was expressed by almost continuous gales of laughter. Alterations in practically all sensory modalities were mentioned, particularly in touch, hearing and vision. As is the case with LSD, distortion of visual perception was outstanding, and involved distance, depth, size, shape and color. Visual distortion usually varied rapidly from moment-to-moment. Perception of elementary visual hallucinations were commonly reported. These entoptic phenomena consisted of colored lights which flickered and coalesced to form patterns varying in a kaleidoscopic fashion, or of shadows that seemed to dance on the wall. In sensitive patients, the lights or shadows were perceived as a definite person, object, or animal which the individual could name. The patients reported increased difficulty in thinking, difficulty in concentration, and in carrying out simple arithmetical calculations or reading. They reported a "rush of thoughts", with one thought replacing another before the first was completed. A feeling of alteration in the individua'ls own body occurred consistently and varied from simple feeling of being light or heavy to marked alterations in size, shape or color. Some patients felt they had become very large,

[1] The nine categories are shown in Table 2. It is of course evident that a large number of other categories could be devised and that there might be many ways of classifying a particular question. There appears to be no easy way out of this difficulty, so the classification must be regarded as completely arbitrary.

Table 1. *Comparison of total course of psilocybin and LSD reactions*

Measure	Placebo	Treatment				
		LSD-25		Psilocybin		
		1.0 mcg/kg	1.5 mcg/kg	57 mcg/kg	86 mcg/kg	114 mcg/kg
Temperature[1] . . .	+ 2,7 ± 0,32	+ 4.8* ± 0.44	+ 4.9* ± 0.48	+ 3.5* ± 0.26	+ 5.7* ± 1.35	+ 4.6* ± 0.26
Pulse rate[1]	+37.8 ± 14.5	+67.3* ± 17.8	+82.8* ± 10.9	+31.9 ± 8.9	+41.6 ± 10.4	+79.1* ± 12.6
Respiratory rate[1] .	+13.1 ± 3.1	+32.9* ± 3.9	+36.7* ± 7.1	+24.5 ± 8.1	+26.4 ± 8.2	+37.5* ± 7.1
Systolic blood pressure[1]	+15.6 ± 13.5	+64.8* ± 10.9	+94.6* ± 17.5	+31.4 ± 12.6	+61.7* ± 11,0	+47.8 ± 16.9
Diastolic blood pressure[1]	−17.5 ± 11.9	+ 9.1 ± 19.1	+35.2* ± 10.7	+ 8.2 ± 9.7	+15.7 ± 11,0	+ 6.6 ± 13.6
Pupillary diameter[1]	0.2 ± 1.4	+10.2* ± 1.18	+15.0* ± 2.1	+ 3.9* ± 0.9	+ 6.0* ± 1.4	+ 5.4* ± 1.9
Patellar reflex[1] . .	+20.7 ± 11.1	−50.9 ± 31.0*	−72.9* ± 21.7	+ 7.1 ± 19.2	−47.6* ± 10.4	−65.5* ± 23.8
No. positive answers[2]	0.1 ± 0.3	57.0** ± 23.2	98.0** ± 26.6	24.0** ± 5.9	38.0** ± 16.3	38.0** ± 11·0
Clinical grade[3] . . .	0 ± 0	2.2** ± 0.38	2.8** ± 0.17	1.2** ± 0.2	1.83** ± 0.4	2.0** ± 0.36

[1] Figures are means ± standard errors (9 subjects) of areas under time-action curves ("degree-hours", "beat-hours", etc.). The signs indicate increases (+) or decreases (−) in the measurement.

[2] Means ± standard errors of number of questions scored positively in the $7^1/_2$ hours after the drug which were not scored positively before the drug.

[3] Means ± standard errors of intensity of mental reaction based on a scale of 0—4.

* Significantly different from placebo ($P<0.05$).

** Significantly different from placebo ($P<0.05$, non-parametric test).

Table 2. *Comparison of pattern of "mental" response after psilocybin and LSD in 9 subjects*

Category *	Number of questions	Total responses possible**	Number of responses in category					
			Placebo	LSD		Psilocybin		
				1.0	1.5	57	86	114
General	7	63	0	25	36	16	23	22
Difficulty in thinking.	4	36	0	10	19	2	8	6
Alteration in mood . .	3	27	0	9	15	3	8	8
Alteration in touch .	4	36	0	11	17	3	4	11
Alteration in hearing .	4	36	0	14	16	6	8	9
Visual distortion . . .	10	40	0	19	31	13	16	19
"Elementary" hallucinations	5	45	0	11	18	5	9	9
"True" hallucinations	4	36	0	5	9	3	2	1
Depersonalization . .	13	117	0	19	33	15	14	18

* Refers to type of questions, e.g., "feeling strange" (general); "feet look old" (depersonalization); "am happy" (mood); "things look small" (visual distortion); "is difficult to concentrate" (thinking), etc.

** Number of subjects times number of questions in the category.

or had shrunk to the size of children. Their hands or feet did not seem to be their own, and sometimes took on the appearance of animal paws. At times, patients had the sensation that they could see the blood and bones in their own body or in that of another person. They reported many fantasies or dream-like states in which they seemed to be elsewhere. Fantastic experiences, such as trips to the moon or living in gorgeous castles, were occasionally reported. Despite these striking subjective experiences, the patients remained oriented in time, place and person. In most instances the patients did not lose their insight, but realized that the effects were due to the drug. Two of the 9 patients, however, did lose insight and felt that their experiences were caused by the experimenters controlling their minds. Reaction usually reached its peak one and one-half hours after the drug was given and remained intense for two to three hours. It subsided almost completely five to six hours after the drug was given. The subjects most frequently compared the subjective experiences after psilocybin to those occurring after LSD or marihuana.

Objective measurements. The data on the objective measurements are shown in table 1. Significant changes as compared with the placebo were observed after both doses of LSD and after one or more of the doses of psilocybin in the cases of rectal temperature, pulse and respiratory rates, systolic blood pressure, pupillary size, and threshold for elicitation of the kneejerk. Thus, psilocybin induced a pattern of autonomic and central nervous system excitation similar to that caused by LSD, but was, of course, less potent than the latter drug.

Subjective measurements. Significant changes, as compared with placebo, occurred after all doses of both drugs, with respect to number

of positive responses on the questionnaire and to the clinical grade. Data on the "pattern of response" is shown in Table 2. When the patterns after the two drugs are compared at the most nearly equivalent doses (1.0 mcgm/kg of LSD, and 114 mcgm/kg of psilocybin) it is evident that the patterns after the two drugs are very similar, except in incidence of "true hallucinations."

The time-course after placebo and the various doses of the two drugs is shown in Tables 3 and 4. The time of onset is very similar after both

Table 3. *Time course of effects of LSD-25 and psilocybin on pupillary size*

Treatment	Hours before or after drug									
	−1	0	+1	+2	+3	+4	+5	+6	+7	+8
Placebo	3.8	3.7	3.9	3.8	3.9	3.8	3.7	3.9	3.9	3.9
LSD, 1.0 mcg/kg . . .	3.8	3.8	4.9	5.4	5.4	5.2	5.2	4.9	4.9	4.8
LSD, 1.5 mcg/kg . . .	3.7	3.7	5.6	6.1	6.1	5.3	5.9	5.6	5.4	5.3
Psilocybin 57 mcg/kg. .	4.1	4.1	4.8	4.4	4.4	4.3	4.3	4.4	4.4	4.6
Psilocybin 86 mcg/kg. .	3.8	3.9	5.1	4.9	4.7	4.7	4.4	4.6	4.4	4.5
Psilocybin 114 mcg/kg .	4.3	4.4	5.8	5.9	5.4	5.1	4.9	4.7	4.6	4.5

Figures are means of pupillary diameter in millimeter on 9 subjects.

Table 4. *Time course of effects of LSD-25 and psilocybin on questionnaire*

Treatment	Hours before or after drug								
	−½	+½	+1½	+2½	+3½	+4½	+5½	+6½	+7½
Placebo	0	0.1	0	0	0	0	0	0	0
LSD, 1.0 mcg/kg . . .	0	3.9	12.3	14.3	13.2	7.4	4.1	1.2	0.6
LSD, 1.5 mcg/kg . .	0	5.1	18.5	19.8	17.7	15.8	10.9	6.8	1.8
Psilocybin, 57 mcg/kg.	0	2.4	5.1	6.3	6.6	2.9	0.6	0.22	0
Psilocybin, 86 mcg/kg.	0	2.0	10.8	10.9	7.9	4.9	0.6	0	0
Psilocybin, 114 mcg/kg	0	6.4	12.6	10.6	6.1	1.9	0.33	0	0

drugs. This result may be, to some extent, an artefact of the fixed observation times, since patients consistently began to report subjective changes sooner after psilocybin than after LSD. Definite pupillary dilatation occurred one hour after both drugs, with the peak effect occurring at one hour after psilocybin and two hours after LSD. As judged by number of responses on the questionnaire, the reaction was beginning to subside by the third to the fourth hour after both drugs, reaching insignificant levels five and one-half hours after psilocybin and six and one-half hours after LSD. The length of action of psilocybin seems definitely shorter than that of LSD.

Comparative potency of LSD and psilocybin. From the data, a number of dose-effect curves comparing the potency of LSD and psilocybin can be constructed. Those based on the total course (pupillary diameter, number of positive responses and clinical grade) yielded estimates that LSD is approximately 100—150 times as potent as psilocybin. Since

the total course of the psilocybin reaction was shorter than that of the LSD reaction these estimates of potency could be misleading. For this reason, change in pupillary diameter at two hours and the number of positive responses at one and one-half hours were calculated and used in constructing the dose-effect curves shown in Fig. 1. Analysis of these data at approximately peak effect for both drugs gave potency estimates with 5 per cent confidence limits of 1 mcgm/kg of LSD being equivalent to 121 (103—156) mcgm/kg of psilocybin in the case of pupillary change,

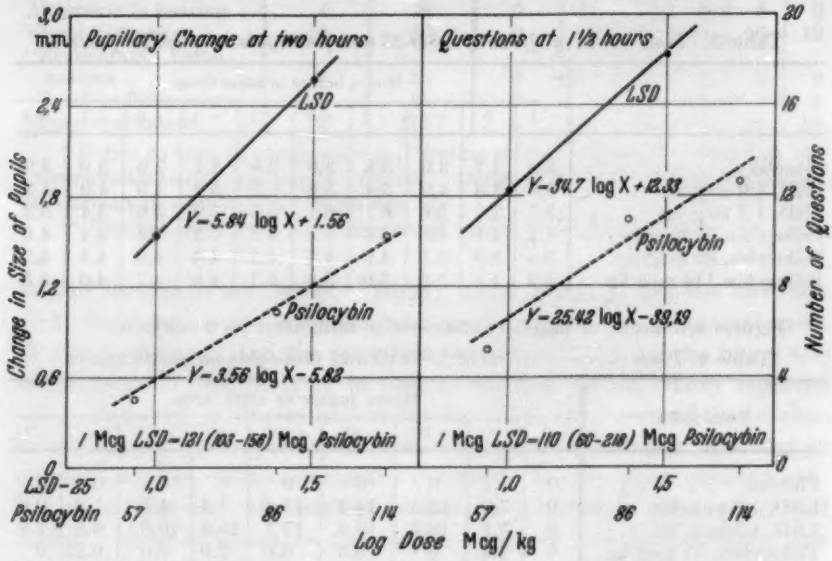

Fig. 1. Relationship of dose of LSD-25 and psilocybin to change in size of pupils and to number of positive responses on the questionnaire

and to 110 (60—218) mcgm/kg in the case of responses on the questionnaire. These two dose-effect curves met the usual tests for parallelism and slope. Unfortunately, the preliminary experiments gave a somewhat high impression of the potency of psilocybin, so that the highest dose of psilocybin used (114 mcgm/kg) corresponded approximately to the lowest dose of LSD (1 mcgm/kg). A dose of psilocybin higher than 114 mcgm/kg and a dose of LSD lower than 1 mcgm/kg would have yielded a more elegant estimate of comparative potency.

Discussion

The reaction observed after oral administration of LSD-25 and psilocybin are remarkably similar. After both drugs, there is evidence of autonomic excitation (elevated temperature, dilated pupils, increased blood pressure and increased respiratory rate) and of increased hyperirritability in the central nervous system (decreased threshold for elici-

tation of the kneejerk). After both drugs, anxiety, difficulty in concentration and thinking, sense of strangeness, marked sensory perceptual distortion (especially visual), alterations in body image (depersonalization), and elementary and true hallucinations occurred. It is, of course, possible that the methods of measurement and the situation in which the experiments were conducted contribute in some degree to this similarity. The subjects had already experienced the effects of LSD, and very likely would expect similar symptoms from any drug given in this particular testing situation. The use of a questionnaire may also suggest certain symptoms. On the other hand, patterns of effects similar to those seen after LSD have not been observed after administration of amphetamine, scopolamine, barbiturates, opiates, chlorpromazine and many other drugs with marked effects on the central nervous system. Thus it seems likely that the similarity between the reactions induced by LSD and psilocybin is a real phenomenon, and suggests that some common biochemical or physiological mechanism is responsible for the effects of the two drugs. Experiments in which subjects tolerant to LSD are challenged with psilocybin and vice versa ("cross tolerance") might help settle the question of the biological identity of the reactions caused by the two drugs.

The similarity in chemical structure of psilocybin and 5-hydroxytryptamine naturally leads one to speculate that psilocybin may cause an abnormal mental state by interfering with the actions, synthesis, disposition or metabolic degradation of 5-hydroxytryptamine. Others have hypothesized that LSD-25, bufotenine and other psychosomimetic drugs might act through such mechanisms. Since psilocybin is a much simpler compound than LSD, it may prove to be an important tool for biochemical studies bearing on the role of serotonin in brain function. Investigations in animals will be necessary to shed light on these possibilities.

Summary

1. The reaction induced by oral administration of 57 to 114 mcgm/kg of 0-Phosphoryl-4-hydroxy-N-dimethyltryptamine (psilocybin) has been compared with that induced by a placebo and LSD-25 (1.0 to 1.5 mcgm/kg) in 9 subjects.

2. Both LSD and psilocybin caused elevations in body temperature, pulse and respiratory rates, and systolic blood pressure. Threshold for elicitation of the kneejerk was decreased by both drugs.

3. After both drugs, abnormal mental states characterized by feelings of strangeness, difficulty in thinking, anxiety, altered sensory perception (particularly visual), elementary and true visual hallucinations, and alterations of body image were reported by the subjects.

4. The effects of psilocybin did not persist as long as those of LSD.

5. LSD is 100 to 150 times as potent as psilocybin.

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The Influence of Side-Effects on the Reporting of Symptoms

By

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With 1 Figure in the Text

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Drug trials in chronic mental hospital patients are open to criticism on two counts. The instigation of a trial normally involves a great increase in the amount of attention paid to the patients, and this by itself, it may be argued, will produce changes in mental state. In preparing a trial with a group of chronic psychotics, we attempted to separate the specific effects of the drug from the general effects of increased attention by imposing the same regime that was to be adopted for the trial well in advance of the beginning of therapy.

In this paper we are concerned with a second point of difficulty which is raised by double blind procedures. This is that many drugs in common use will betray themselves by their physical effects, and thus allow opportunity for the expression of any bias that the observer may have for or against the drug. While this difficulty has been recognised it appears to have been the subject of speculative rather than experimental enquiry.

The experiment described here was undertaken to clarify three points:

1. If a drug has recognizable physical side-effects, how accurately and how rapidly are they likely to be detected ?

2. What effect if any will the detection of side-effects have on the reporting of other symptoms ?

3. Will the detection of side-effects lead to differences in assessment of mental state ?

The trial was carried out with a group of 28 chronic psychotics, whose condition had remained unchanged during a preliminary period of assessment lasting 3 months, and a further period of 2 months while the full regime to be adopted in the trial was in force. The findings may not apply to other classes of patients.

Half this group (14 patients) were given an inert placebo (Lactose) while the other half received small doses of nicotinic acid. This substance was chosen because it is unlikely in small doses to produce any change in mental state, but it has an obvious somatic effect, which should lead to its detection in a majority of those receiving it. The effect is a tran-

sient flushing of the skin, particulary of the face and neck, accompanied by a sensation of heat and sometimes by irritation of the skin. This appears generally within 30 minutes of oral administration and disappears in a further half hour.

For the trial to be experimentally valid it is necessary to ensure that the substance chosen shall not itself exert any therapeutic effect. This possibility cannot be completely ruled outh with any drug that is physiologically active, but the evidence (reviewed by GREGORY 1955) suggests that any effect to be anticipated from nicotinic acid would be by correction of an unrecognised deficiency state rather than by a direct action on the psychosis. The hospital diet did not appear to be deficient in nicotinic acid, but as an additional safeguard the diet was supplemented with 'Marmite' for eight weeks before the start of the trial. The 'Marmite' was given as a hot drink twice daily and in soups, stews, and gravy, in amounts sufficient to cover twice the daily requiements of nicotinic acid.

Methods

Patients. The patients were 28 chronic male psychotics. They formed part of a larger group housed together in a hospital annexe in which an open-door regime had been in operation since 1941. The selection of patients was based on age (less than 65), chronicity (oven 15 years in hospital), absence of recent psychiatric treatment (for at least 5 years) and diagnosis (chronic schizophrenia or depression, without signs of organic brain disease). As mentioned above these patients had been observed for a total of five months before the initiation of the trial, and all who showed fluctuations in mental state excluded.

They were matched for age, length of hospitalisation and severity (assessed on a five-point scale). Patients were then allotted to one or other of two groups by a random method, and one was chosen as the experimental group by tossing a coin.

Dosage and mode of administration. The experimental group were given 100 mg of nicotinic acid by mouth daily. It was given in powder form, mixed with enough lactose to fill two gelatine capsules. It was administered in a single dose after breakfast.

The control group received lactose, similarly dispensed and administered.

Each patient had his own supply of capsules in a separate container, replenished weekly.

In addition to the crucial morning dose, in which alone the two groups differed, all patients were given two further doses of placebo capsules during the day. This was done simply in order to maintain the schedule of dosage which had been designed for trial of other drugs at a later stage.

Timetable for trial. Patients were given a high nicotinic acid diet, as already stated, for eight weeks immediately before the trial. Also, during this period, they received 6 placebo capsules daily, and a routine of twice-weekly interview and examination was established.

The initiation of the trial was not marked by any overt change in routine, and no warning was given to the nursing staff that there had been any alteration in treatment.

The trial lasted for nine weeks. Subsequently all were again given lactose placebos.

Instructions to nursing staff. The nursing staff were told that a clinical trial of a new preparation was to be conducted. They were given no indication of its nature; nor were they told how many patients were receiving the drug, nor when the supposed treatment started or ended.

They were questioned about each patient before, during, and after the nine week period of the trial, with particular reference to changes in habits, amount of activity, and occupation.

In addition they were asked to report at once the occurrence of any unusual signs or symptoms. A number of likely ones were listed, including flushing, and they were asked to watch particularly for these. The full list was: giddiness, nausea or vomiting, headache, paleness or flushing, drowsiness, fits or faints, loss of appetite, abdominal pain, jaundice, and restlessness.

The two senior nurses who took part in the trial had worked for many years in the annexe, and knew the patients extremely well.

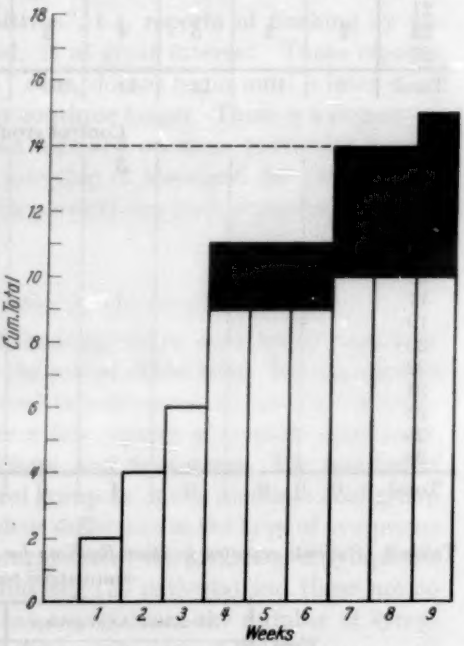

Fig. 1. Number of patients reported to show flushing. Cumulative weekly totals. White columns = Nicotinic Acid group. Black columns = Controls

Findings

1. Reports of flushing

Table 1 shows the number of reports of flushing for each patient made by the nurses during the nine weeks of the trial. Ten patients in the nicotinic acid group together accounted for 96 reports: over half of

Table 1. *Reports of flushing.* Weekly incidence and totals

Patient	Week									Total
	1	2	3	4	5	6	7	8	9	
Nicotinic acid group										
1							1			1
3										0
5				1						1
7										0
9				3	2	1	1			7
10	1	2	5	4	2	5	5	3	5	32
13		3				2		1	2	8
14			1							1
15			2							2
16		2	1		2	1		3	2	11
18				2	1	1				4
21										0
23	1	3	5	4	3	4	4	3	2	29
27										0
Total	2	10	14	14	10	14	11	10	11	96
Control group										
2				3		4	2	1	1	11
4										0
6										0
8										0
11										0
12										0
17				1			1		1	3
19										0
20							1			1
22										0
24									1	1
25										0
26										0
28							1			1
Total	0	0	0	4	0	4	5	1	3	17

Table 2. *Patients reported to show flushing for the first time.* Weekly incidence and cumulative totals

Week	Nicotinic Acid group		Control group	
	Number of patients	Cumulative total	Number of Patients	Cumulative total
1	2	2	0	0
2	2	4	0	0
3	2	6	0	0
4	3	9	2	2
5	0	9	0	2
6	0	9	0	2
7	1	10	2	4
8	0	10	0	4
9	0	10	1	5

these related to two patients. 17 reports, relating to five patients were made in the control group.

Table 2 shows the number of patients in each group reported to show flushing *for the first time*, and the cumulative totals of patients recognised in this way, for each week of the trial. The cumulative totals are shown as a histogram in Fig. 1. The white columns represent patients in the nicotinic acid group, the black columns controls.

It is evident that the recognition of side-effects may be considerably delayed. Throughout the trial there was slow but progressive recognition of the members of the nicotinic acid group. Only two were detected in the first week, and fresh cases continued to be reported up to the seventh week, after which the total remained stationary. By this time ten out of the 14 patients receiving nicotinic acid had been recognised.

The occurrence of "false-positives", i.e. reports of flushing by patients not receiving nicotinic acid, is of great interest. These reports, by comparison with the "correct" ones, do not begin until a later stage of the trial (fourth week) and they continue longer. There is a suggestion here that once attention has been focussed on some particular feature of the situation, there may be a lowering of threshold for this feature, so that instances are reported which would not have attracted notice in normal circumstances.

2. Reports of other symptoms and signs

In addition to the reports of flushing, there were many reports of other signs and symptoms during the period of the trial. The commonest were reports of noisiness or unusual talkativeness, or, on the contrary, of unusual quietness. There were a few reports of somatic symptoms, including headache, nausea, giddiness, and drowsiness. The number of reports was the same in the control group as in the nicotinic acid group (39 in each), and there was no evident difference in the type of symptoms in the two groups. However, a comparison of the incidence of symptoms between those reported to show flushing (15 patients) and those not so recognised (13 patients) reveals that nearly twice the number of symptoms related to the former group (50 reports against 28).

Table 3 shows the incidence of flushing and of other symptoms week by week during the trial. For comparison, the incidence of other symptoms is also shown for eight weeks before the trial and eight weeks after. For the first three weeks of the trial other symptoms are not reported more frequently than in the preceding eight weeks, despite the incentive provided by the instructions to the nursing staff. In the fourth week, there is a marked increase, and for the remainder of the trial the number of reports continues to be raised by comparison with the pre-trial

Table 3. *Reports of flushing compared with reports of other signs and symptoms.* Weekly incidence and totals

Week	Flushing	Other signs and symptoms	Week	Flushing	Other signs and symptoms	Week	Flushing	Other signs and symptoms
8 weeks immediately before start of trial	0	0	1	2	2	8 weeks after the trial	0	1
	0	3	2	10	3		0	1
	0	1	3	14	7		0	1
	0	4	4	18	24		0	1
	0	5	5	10	8		0	2
	0	4	6	18	12		0	0
	0	1	7	16	9		0	0
	0	5	8	11	7		0	0
			9	14	6			
Total	0	23	Total	113	78	Total	0	6

period. This increase is not accounted for by any change in symptomatology: the same symptoms are reported but more frequently than before. The fact that this occurs in the fourth week, at the same time that "false-positive" reports of flushing began to be made, perhaps lends support to the idea that there was a change in awareness at this time. This is readily understandable when it is remembered that many of these patients had been observed without change by the same nurses for many years. The occurrence of even trivial changes, in the setting of expectation aroused by a clinical trial, may revive interest, and lead to more extensive reporting. At the end of the trial, when reports of flushing ceased to be made, the reports of other symptoms fell to, or even below the original level.

3. Effect on nurses' assessments of patients

From the foregoing sections it may be surmised that one effect of drugs which produce somatic side-effects is to cause increased attention to be paid to those patients who show these changes. The next question is whether this will introduce any bias into the assessment of mental state.

In Table 4 are shown the nurses' assessments of mental state, classed as improved, no change or worse. Table 4 (i) shows the comparison between nicotinic acid and control groups: Table 4 (ii) that between patients who were reported to show flushing and those who were not. Neither comparison reveals any appreciable difference.

Similar comparisons were made with nurse's ratings of certain aspects of ward behaviour (eating habits, toilet habits, occupation, social activites), and here likewise no differences were found.

Ratings by the two experimenters on the general state of the patients and on several specific features of their mental condition (Speech, Delusions, Hallucinations, Response to Commands, Orientation, and General Information) were also examined. These ratings cannot be treated on the same basis as the nurses' ratings, since the experimenters knew the nature and purpose of the investigation (though they did not know which patients had been allotted to the two groups). For what it is worth, the absence of any appreciable change in these ratings may be regarded as confirmation that the mental status of patients had not in fact altered.

Table 4. *Nurses' assessments*

	Improved	No change	Worse	Total
(i) Comparison between nicotinic acid and control group				
Nicotinic Acid	3	9	2	14
Control . . .	4	8	2	14
(ii) Comparison between patients reported and not reported to show flushing				
Flushing. . .	4	8	3	15
No flushing .	3	9	1	13

Discussion

This experiment may be regarded as a model of the double blind trial: it is in fact a replica of such a trial under conditions when the drug which is under examination does not produce the desired effect (improvement in mental state) but does produce recognisable side-actions.

We may consider the results as a demonstration of how observers in a clinical trial may build up a picture—not necessarily explicit—of the effects of a drug. The development of this picture when there are genuine and detectible signs of the drug is a gradual process, and it follows a certain pattern. In the present instance there was an initial delay before side-effects were recognised at all. They were noticed first in patients who were receiving the drug. At a later stage similar side-effects were reported in patients not receiving the drug. Also, at this stage of the trial, there was an increase in the number of reports of other signs and symptoms. This increase occurred particularly in patients who had been reported to show flushing. It was equally marked in the nicotinic acid and control groups. A possible interpretation of these findings is that the occurrence of somatic change stimulates an increase in awareness which acts in two ways. It shows itself first as a readiness to discern the same change in other patients, and secondly in an increased interest in those patients who show the change.

It seems clear that distortions of this kind may enter into the reporting of observations. A separate question is how far these distortions affect the formation of judgements about the outcome of treatment. The argu-

ment for imposing double blind conditions is that if the observers are not told which patients are receiving the drug they cannot be influenced by prejudice for or against it. They cannot however be prevented from making guesses, based on their own observations, and when this happens, three possibilities are open.

1. They may guess correctly in every case. The double blind procedure is then useless, and provides no safeguard against the operation of prejudice. (Formally, there is also the possibility that they guess wrongly in every case).

2. Their guesses may be distributed at random. This appears to be the only condition in which the procedure is valid.

3. They may guess either more correctly or more wrongly than chance. This is the possibility realised in the present trial, and one might suspect the usual state of affairs. In this case, the double blind procedure would appear to be invalidated to a greater of lesser extent depending on the degree of departure from chance.

It does not of course follow, because there is scope for the operation of prejudice, that prejudice will necessarily be shown. Thus in the present experiment the final assessments of patients by the nurses was not apparently affected by the observation of side-effects. This may be because they were in fact unprejudiced, or it may be because their prejudice was in a conservative direction, and they would equally have failed to recognize a genuine alteration if it had occurred.

It seems likely that the selective reporting of observations, in conformity with a pattern constructed by the observer, will not be confined to chronic patients such as the group studied by us: though it may well be that in a group of acute patients or those of rapidly varying mental state, the selective process would take different forms. Whether in these circumstances, judgements about the outcome of treatment would still be unaffected, is an open question, which requires empirical determination.

If further experiments confirm the present findings, it may be necessary to consider whether the double blind procedure is not a self defeating one. It may be better that the observers, at any rate, should know what they are meant to be doing. Alternatively, it may be possible to retain the procedure, but alter the design to take advantage of information about the opinions which the observers have formed as to which patients are receiving an active preparation. The key comparison would then lie between patients having a drug but not thought to be, and those not having it but thought to be. Certainly, a trial in which the former were found to do better than the latter would provide strong evidence for the efficacy of any drug.

Summary

A dummy trial was carried out with the object of investigating the effect of the physical side-effects of treatment on the assessment of its results.

During a period of nine weeks, fourteen chronic psychotic patients were given small doses of nicotinic acid by mouth, with the object of inducing a recognizable physical change (flushing) without change in mental state. Fourteen matched controls were given placebos under the same conditions.

Nursing staff were told nothing about the nature of the trial but were asked to report the occurrence of certain signs and symptoms which included flushing.

Ten patients out of 14 receiving nicotinic acid were reported to show flushing. Flushing was also reported in five patients not receiving nicotinic acid. These "false-positive" reports occurred at a later stage of the trial than the correct ones. Concomitantly there was an increase in the number of reports of other symptoms. Such reports were twice as common in patients who also showed flushing, but were equally distributed between the nicotinic acid and control groups.

It is suggested that during a clinical trial the occurrence of side-effects enables a picture to be built up of which patients are receiving the active drug. This picture may be correct, or it may be wholly or partially erroneous, but unless it is completely random it contradicts the assumptions underlying the use of the blind trial.

The occurrence of side-effects also stimulates the interest of observers and leads to an increase in the reporting of other symptoms, particularly in those patients in whom side-effects are observed.

The final assessment of patients was not affected, despite the inefficacy of the double blind precaution.

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Etude psychométrique des effets de l'amobarbital (amytal) et de la chlorpromazine sur des sujets normaux

Par

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(Manuscrit reçu le 7 février 1959)

Introduction

On admet de plus en plus communément aujourd'hui, et naturellement surtout en psychiatrie, qu'entre la pharmacodynamie animale classique et la thérapeutique clinique, il y a lieu de procéder à une étude expérimentale humaine des médicaments.

Cherchant à développer la caractérisation des diverses classes de psycholeptiques et en particulier les différences entre neuroleptiques phénothiaziniques et hypnotiques barbituriques que l'un de nous a soulignées maintes fois, nous avons été frappés par le petit nombre des études psychométriques, surtout si l'on élimine celles qui ont été conduites exclusivement sur de grands malades, schizophrènes en général; et nous avons été ainsi amenés à entreprendre nous-mêmes une comparaison expérimentale des effets de la chlorpromazine et de l'amobarbital (amytal) qui est sans doute le barbiturique considéré actuellement comme le plus susceptible d'entraîner des changements psychologiques importants et le plus utilisé à cet effet, en particulier dans les narcoanalyses.

La revue des travaux antérieurs au nôtre se trouve détaillée dans la thèse de Nicolas-Charles (1958); nous n'en donnerons ici que le résumé.

En ce qui concerne les barbituriques, on ne peut que citer rapidement, bien qu'ils ne soient nullement négligeables, les travaux d'Oehler (1931), de Ranschburg (1934), de Peter (1939), de Sargant et Slater (1942), de Trent (1947), d'Arkola (1947), de Berg (1949) et même ceux de Grunewald (1954) et d'Idestrom (1954) et de Lehman et Csank (1957) qui ont étudié les variations de la performance à telle ou telle épreuve sous l'influence de tel ou tel barbiturique.

Landis et Zubin (1951) avec le phénobarbital ont conduit sur des sujets normaux une étude plus vaste et surtout très précise. De tous ces travaux hétérogènes résulte cependant une impression globale: le déficit serait d'autant plus sévère que l'on se trouve aux plus bas niveaux de l'« échelle psychologique », c'est ainsi que la détérioration est nette pour l'ergographie, le tapping, la discrimination du papillotement

lumineux, qu'elle est beaucoup plus discutable pour les temps de réaction, surtout dans les épreuves complexes de choix et que si elle existe elle est très difficile à mettre en évidence dans les tests de facteur G. Cette impression corrobore l'observation minutieuse d'un cas d'intoxication chronique publié en 1934 par COHEN, SEARS et SHIPLEY.

Si l'on considère l'éventualité de remaniements affectifs, de variations instinctuelles et leurs conséquences sur les épreuves dites de personnalité, nous nous trouvons devant une série d'études encore plus disparates. La plupart d'entre elles toutefois utilisent la situation bien spéciale, «subaiguë» peut-on dire, de l'injection intra-veineuse d'une dose (amobarbital le plus souvent) qui altère l'état de la conscience; il en est ainsi pour celles de LINDEMANN (1932), d'EYSENCK (1945), d'IRÈNE ROUBLEFF (1949), de WARSHAW (1954), de WEINSTEIN et MALITZ (1954). KORNETSKY, en 1951, met en évidence la baisse du contrôle du MOI dans l'intoxication chronique; MUECHER en 1953 attire justement l'attention sur l'influence de la nature du barbiturique: l'hexobarbital si actif sur les fonctions sensori-motrices n'a que des effets négligeables en regard de ceux du barbital («Véronal») sur les sentiments de frustration; il faut enfin faire une place spéciale aux recherches complexes et difficilement résumables de HILL, BELLEVILLE et WIKLER (1957), qui, à l'occasion de la mesure de temps de réaction, ont cherché à mettre en évidence l'influence de la motivation sur l'activité psychophysiologique de diverses drogues et réciproquement (schématiquement le pentobarbital allonge fortement les temps si la motivation est faible et tend à les raccourcir si elle est forte). Aucune conclusion ferme ne semble se dégager de cet ensemble; l'excès de l'action globale souvent provoqué par l'administration intra-veineuse, ne permettant pas la discrimination fine de changement d'attitudes (et gênant l'application large à des sujets normaux), et le défaut d'un instrument métrique suffisamment précis, objectif et maniable, semblent les deux principales sources de cette incertitude.

En ce qui concerne les phénothiazines, nous ne connaissions, lorsque nous avons entrepris notre travail, que les publications de HEIMANN (1955), d'ERNST (1954), de SUTTER et PASCALIS (1956) et de LEHMAN et CSANK (1957); il semblait en résulter que la chlorpromazine respecte les fonctions intellectuelles tout en altérant d'une part les fonctions élémentaires psycho-physiologiques et d'autre part l' «allant» (*Zuwendung*) et la spontanéité pulsionnelle (*Antrieb*); mais ces résultats ne paraissaient étayés que sur peu d'observations et dans des conditions parfois discutables.

Méthode

Devant les lacunes de la littérature, nous avons conçu l'idée d'une expérience où les mêmes sujets, normaux, absorberaient chacun suc-

cessivement de la chlorpromazine, de l'amobarbital et un placebo et où, en même temps qu'ils fourniraient leurs impressions brutes, ces sujets seraient soumis à une série de tests variés permettant de comparer, dans le plus large domaine possible, les effets des deux médicaments.

1. Organisation de l'expérience. Nous nous sommes adressés à dix-huit sujets volontaires, douze hommes et six femmes, de 24 à 32 ans, de nationalité française, de race blanche, médecins ou étudiants en médecine âgés, ne présentant aucune anomalie mentale cliniquement évidente et fournissant des profils non pathologiques au MMPI. Ils étaient avertis qu'ils étaient conviés à expérimenter trois sédatifs et qu'ils ne devaient s'attendre à aucun effet extraordinaire ou nocif mais qu'ils risquaient d'éprouver un certain endormissement dans les heures qui suivraient l'ingestion; à chaque séance ils ignoraient naturellement la nature du comprimé ingéré.

Nous avons imposé un horaire uniforme à tous les sujets pour toutes les séances; l'intervalle entre deux séances consécutives pour le même sujet a été en moyenne d'une semaine. Afin d'éliminer les effets d'apprentissage et plus généralement de test-retest, nous avons réparti l'ordre de passation des trois drogues entre les dix-huit sujets selon les six permutations (au sens arithmétique) de trois, chacune étant donc utilisée par trois sujets.

La posologie a été fixée à cent milligrammes de chlorpromazine et trois cents milligrammes d'amobarbital. La dose était répartie en trois prises égales d'un comprimé à absorber respectivement quatre heures, deux heures et une demi-heure avant le début de la séance. Quelques petites perturbations (sécheresse de la bouche, ralentissement moteur) ont souvent été notées par les sujets mais il n' y a eu à relever aucun incident véritable.

2. Constitution de la batterie. La batterie, dont l'administration durait environ deux heures, comprenait un certain nombre de mesures psychophysiologiques et de tests psychométriques variés et enfin un questionnaire qui exigeait des sujets une évaluation quantitative de leur état subjectif dans des directions précises:

1. Mesure de la vitesse de la frappe digitale (tapping) en enregistrant électriquement le nombre de coups de stylets donnés pendant vingt secondes, de la main préférentielle; le résultat était la moyenne de quatre mesures successives, désignée par V.

2. Mesure de la vitesse et de la précision de la frappe sur des points déterminés. Dans cette épreuve empruntée à Shatin et Rockmore, le sujet devait frapper successivement au fond de trois trous de trois millimètres de diamètre, disposés aux sommets d'un triangle équilatéral de 86 millimètres de côté. Les frappes correctes, W, et les frappes erronées, e, étaient enregistrées séparément; on calculait ensuite le

pourcentage des secondes par rapport aux premières; là aussi on retenait la moyenne de quatre épreuves de vingt secondes.

3. Mesure du temps de réaction manuelle à un stimulus auditif; on notait la moyenne et l'écart-type des trente meilleures parmi trente-deux mesures successives, opérées à l'aide d'un appareil à déclenchement automatique donnant des coups de timbre irrégulièrement espacés.

4. Test de facteur G de Cattell (*Culture Free Test*) série III. Afin de constituer trois versions parallèles nous avons découpé la forme A, par séparation des items pairs et impairs, en deux sous-formes A1 et A2 auxquelles nous avons ajouté une sous-forme B1 obtenue par le même procédé; les temps de passation étaient en conséquence réduits de moitié.

5. Test de rétention visuelle (V.R.T.) de Benton; nous avons utilisé les trois formes paralèlles C, D, E, établies par l'auteur.

6. Test des labyrinthes (*Maze Test*) de Porteus. Nous avons dû, pour obtenir nos trois formes, procéder à un découpage assez complexe des versions «Vineland 1933» et «Extension», dont nous ne pouvons exposer le détail ici.

7. Mesure de l'empan mnésique par la remémoration immédiate de chiffres (*Digit Span*).

8. Epreuve de production d'une durée. Par deux «top» le sujet délimitait un intervalle silencieux qu'il considérait comme égal à vingt secondes; l'expérimentateur notait au chronomètre la durée réelle de cet intervalle.

9. Inventaire Multiphasiquede Personnalité du Minnesota, MMPI., dans son adaptation française.

10. Questionnaire de sensibilité de Robinson et Freeman transposé sous formes d'assertions écrites mêlées au MMPI dont elles ne se distinguaient pas pour le sujet.

11. Questionnaire original à choix forcé multiple; nous présentions au sujet trois échelles graduées de —3 à +3 et matérialisées avec leur signification sur du bristol; l'échelle de Vigilance (V) permet d'exprimer le besoin plus ou moins grand de dormir ou au contraire l'impression d'être particulièrement éveillé; l'échelle d'Humeur (H) concerne d'éventuels sentiments d'euphorie ou de dépression; l'échelle de Tension (T) est relative à la sensation d'énervement ou de détente; le zéro correspond à l'état habituel personnel du sujet aux mêmes heures de la journée et les notes +3 et —3 au maximum de déviation qu'il pense pouvoir éprouver. Après s'être assuré que le sujet a bien compris la signification des échelles et leur graduation, on l'invite à se situer sur chacune d'elles en inscrivant lui-même le chiffre choisi après le temps de réflexion qu'il désire.

Nous avons demandé à nos sujets deux notes par échelle, la première correspondant à leur état au début de la séance (note D), la seconde à leur état actuel en fin de séance (note F).

3. Traitement des résultats. Pour chaque résultat, nous disposions finalement de cinquante-quatre notes réparties sur un tableau rectangulaire à dix-huit lignes et trois colonnes; nous avons établi la moyenne de chaque distribution et testé les trois différences par le t de Student. Comme il s'agissait d'une étude d'orientation, nous avons été relativement peu exigeants et nous avons retenu même les différences significatives seulement à · 10. Quelques coefficients de corrélation (Bravais-Pearson) ont été calculés bien que leur intérêt soit faible avec 18 sujets seulement.

Résultats

Les résultats sont exposés dans cinq tableaux:

Dans ces tableaux nous avons utilisé les abréviations suivantes:

m = note moyenne
t = t de Student
r = coefficient de Bravais-Pearson
n. s. = différence pas même significative à . 10
* = différence significative à . 10
** = différence significative à . 05
*** = différence significative à . 20
**** = différence significative à . 01

Tableau n° 1. *Résultats du questionnaire*

Echelle	Note moyenne m			t des différences			r
	Am.	Pl.	Chl.	(A—P)	(C—P)	(A—C)	
Vigilance							
début .	−0,72****	−0,28*	−0,95****	*	****	n.s.	n.s.
fin . . .	−1,17****	−0,33*	−1,67****	****	****	n.s.	0,45*
(F—D) .	n.s.	n.s.	**				
Tension							
début .	−0,06 n.s.	+0,28*	−0,39*	n.s.	**	n.s.	0,42*
fin . . .	−0,56*	−0,17 n.s.	−0,56**	n.s.	n.s.	n.s.	0,43*
(F—D) .	**	**	n.s.				
Humeur							
début .	+0,28 n.s.	+0,06 n.s.	−0,11 n.s.	n.s.	n.s.	n.s.	n.s.
fin . . .	+0,39 n.s.	+0,17 n.s.	−0,06 n.s.	n.s.	n.s.	n.s.	n.s.
(F—D) .	n.s.	n.s.	n.s.				

N. B.: r est ici le coefficient de corrélation entre l'effet de l'amytal (A—P) et celui de la chlorpromazine (C—P).

Tableau n° 2. *Résultats des mesures psychophysiologiques*

Nature de la mesure	m			t des différences			
	Am.	Pl.	Chl.	(A—P)	(C—P)	(A—C)	
Frappe digitale							
v	138,0	145,3	135,8	****	****	*	
w	26,85	28,22	27,13	****	**	n.s.	
$\frac{e}{W} \times 100$	58,7	65,2	67,9	n.s.	n.s.	*	
Temps de réaction (en ms.)							
Temps moyen	236	232	241	n.s.	n.s.	n.s.	
écart-type	31,7	30,3	30,9	n.s.	n.s.	n.s.	

Tableau n° 3. *Résultats des tests psychométiques à l'exception du M M P I*

Test	m			t des différences		
	Am.	Pl.	Chl.	(A—P)	(C—P)	(A—C)
Cattell G . . .	13,5	13,3	13,9	n.s.	n.s.	n.s.
Benton	7,7	7,8	7,7	n.s.	n.s.	n.s.
Porteus						
Note	7,3	7,2	7,3	n.s.	n.s.	n.s.
Note Q . . .	6,2	6,4	6,0	n.s.	n.s.	n.s.
Mémoire des chiffres . . .	7,1	6,8	6,9	n.s.	n.s.	n.s.
Durée produite (en secondes)	18,3	17,2	17,7	*	n.s.	n.s.
Robinson . . .	+5,0	+5,13	+5,66	n.s.	n.s.	n.s.

Tableau n° 4. *Résultats du M M P I sauf l'échelle Mf*

Echelles	m			t des différences		
	Am.	Pl.	Chl.	(A—P)	(C—P)	(A—C)
?	5,61	5,94	5,66	n.s.	n.s.	n.s.
L	5,33	5,61	5,30	n.s.	n.s.	n.s.
F	4,94	4,44	5,00	n.s.	n.s.	n.s.
K	16,44	16,28	15,72	n.s.	n.s.	n.s.
Hs	11,61	11,11	11,56	n.s.	n.s.	n.s.
D	20,05	19,50	19,89	n.s.	n.s.	n.s.
Hy	18,16	17,39	17,22	n.s.	n.s.	n.s.
Pd	20,11	20,89	19,94	n.s.	n.s.	n.s.
Pa	7,28	6,94	6,78	n.s.	n.s.	n.s.
Pt	25,83	24,67	24,89	n.s.	n.s.	n.s.
Sc	26,33	24,05	23,67	***	n.s.	***
Ma	18,83	17,00	17,39	***	n.s.	***
Mf	(Cf. tableau 5)			***	n.s.	**
Si	32,2	31,3	32,1	n.s.	n.s.	n.s.
Ca	10,05	9,17	10,11	**	n.s.	n.s.
Indices (F—K)	−11,50	−11,83	−10,71	n.s.	n.s.	n.s.
AI	60,1	58,2	59,6	n.s.	n.s.	n.s.
IR	101,4	101,1	102,9	n.s.	n.s.	n.s.

Tableau n° 5. *Résultats de l'échelle Mf du M M P I*

Echelle Mf	m			t des différences		
	Am.	Pl.	Chl.	(A—P)	(C—P)	(A—C)
12 H.	22,3	23,4	23,7			
6 F.	35,3	32,5	32,2			
Total				***	n.s.	**

N. B.: Dans le calcul des variations moyennes on a bien entendu inversé le signe des variations féminines de façon à mettre en évidence le renforcement des attitudes respectives de chaque sexe sous amobarbital.

Discussion

Les principales remarques qu'appellent ces résultats peuvent être condensées ainsi:

1. Effets subjectifs. Sous placebo les sujets se sont trouvés légèrement endormis; cet effet est dû à l'impression de somnolence accusée par six sujets, soit le tiers, proportion habituelle des «placebos suggestibles».

Les deux produits actifs ont eu un effet hypnotique significativement supérieur à celui des placebos, effet qui s'est accentué en cours de séance.

Entre les deux produits la corrélation est assez médiocre et la différence enregistrée en faveur d'une action hypnotique plus forte avec les 100 mg de chlorpromazine qu'avec les 300 mg d'amobarbital n'est pas statistiquement significative.

En début de séance, les sujets qui n'ont eu qu'un placebo se sentent plus «tendus» que normalement, mais se «détendent» au fur et à mesure des épreuves. Les sujets qui ont absorbé de la chlorpromazine arrivent au contraire nettement «détendus». Sous amytal l'effet de détente est moins évident et plus lent; il n'y a là aussi qu'une corrélation médiocre entre les effets des deux produits actifs.

Les résultats aux échelles d'humeur suggèrent une action légèrement euphorisante de l'amytal et une action légèrement dysphorisante de la chlorpromazine, mais ces différences ne sont pas statistiquement significatives.

Ajoutons qu'on ne trouve entre les trois échelles que des corrélations faibles ou nulles, sauf en début de séance où l'on trouve entre H et V:

$r = 0{,}61$ pour (A—P)
$r = 0{,}41$ pour (C—P)

ce qui suggère que l'action hypnotique et l'action euphorisante attribuées à l'amobarbital sont peu compatibles et ne relèvent pas du même processus.

2. Mesures psycho-physiologiques. Les résultats du tableau n° 2 sont de lecture facile. Les produits actifs n'ont pas entraîné d'allongement significatif des temps de réaction, ni modifié la dispersion des essais successifs. La vitesse du tapping a été ralentie, de façon modérée mais hautement significative, quasi constante, et nettement plus par les 100 mg de chlorpromazine que par les 300 mg d'amobarbital; on est tenté d'établir un lien entre ce résultat et la baisse subjective de vigilance rapportée plus haut, mais le calcul n'a montré aucune corrélation entre les deux phénomènes. Enfin dans la frappe avec visée, le ralentissement est le même avec les deux produits, mais le pourcentage d'erreur est moindre avec l'amobarbital.

3. Mesures psychométriques. On voit qu'il n'y a aucune modification aux épreuves à prédominance intellectuelle, ni d'ailleurs au question-

naire Robinson-Freeman. L'épreuve de production de durée enregistre pour l'amobarbital une variation traduisant un raccourcissement du temps subjectif; mais cette variation est faiblement significative et ne tire son intérêt que d'un certain parallélisme avec les variations enregistrées au MMPI.

Ajoutons que l'étude des notes des trois premiers tests, classées par rang de séance, nous a montré la validité des découpages que nous avions été obligés de faire.

4. MMPI. On constate que:

1. Entre la chlorpromazine et le placebo il n'y a ni variation significative à une ou plusieurs échelles, ni tendance globale à l'élévation ou l'abaissement du profil.

2. Avec l'amobarbital au contraire, le profil est dans l'ensemble plus élevé que sous placebo ou sous chlorpromazine et cette variation devient hautement significative (à · 02) pour les échelles Sc, Ma et Mf.

L'élévation de Ma et Sc ne dépend ni de K, ni des questions communes aux deux échelles brutes, mais bien des parties indépendantes de celles-ci. En outre, on ne peut objecter la facilité de trouver, sur un tel nombre d'échelles, quelques-unes qui présentent des variations «significatives»; le calcul montre que, sur l'ensemble des huit échelles nosologiques, la probabilité d'en trouver deux qui, par le simple jeu des facteurs aléatoires, présentent des variations «significatives» à · 02 est à peine supérieure à 1 %.

Pour l'échelle Mf dont le principe est différent et dont l'interprétation est délicate dans un groupe réunissant les deux sexes, il faut retenir que les six notes féminines sont toutes plus élevées sous amobarbital que sous placebo ou sous chlorpromazine tandis que la moyenne des douze notes masculines est au contraire plus basse.

Signalons enfin l'élévation, toujours sous amobarbital, mais significative seulement à · 05, de l'échelle de caudalité de Williams et soulignons l'absence de variation de l'indice d'anxiété et du coefficient d'intériorisation de Welsh.

Conclusions

Deux ordres de conclusions se dégagent de l'ensemble de nos résultats.

Tout d'abord les mesures psycho-physiologiques et les tests intellectuels nous confirment pour l'amobarbital de façon très évidente ce que la littérature nous faisait entrevoir pour l'ensemble des barbituriques: le déficit aux épreuves de performance est d'autant plus marqué qu'elles sont plus élémentaires, sensori-motrices, d'autant plus faible, jusqu'à être pratiquement nul, qu'elles sont plus rationnelles, noétiques. Nous pouvons en outre étendre ce schéma à la chlorpromazine dont en première approximation les effets ne sont pas qualitativement différents; il est vraisemblable qu'il s'agit là d'un schéma général d'action des psycholeptiques.

Au contraire, le test de personnalité utilisé montre une importante différence entre les deux médicaments. Tandis que la chlorpromazine est pratiquement inactive sur le MMPI, l'amobarbital entraîne des modifications limitées mais nettes de l'ensemble du profil et surtout de certaines échelles; quelle que soit la difficulté d'interpréter ces modifications, leur mise en évidence est du plus haut intérêt.

En effet, une troisième conclusion, méthodologique, s'impose: il est possible, même par des tests où le sujet verbalise ses attitudes, de faire apparaître les variations infra-cliniques de celles-ci sous l'influence de doses minimes, ambulatoires, de sédatifs. L'intérêt de constater des changements d'attitude même minimes et de découvrir une méthode capable de les mesurer est multiple; il est primordial pour le médecin si l'on admet, comme l'un de nous le proposait en conclusion d'un colloque international consacré à la chlorpromazine, que la véritable voie paraît être dans l'aide que les médicaments peuvent introduire dans la recherche de nouveaux contacts humains, d'une nouvelle approche du malade.

Summary

The authors sought to develop knowledge of the characteristics of different types of psycholeptic drugs. Using 18 normal volontary subjects, and psychometric methods, the authors experimentally compared the effects of the following: a dose of 100 mg of chlorpromazine (neuroleptic), a dose of 300 mg of amobarbital (hypnotic) and a placebo.

The psychophysiological measures and intelligence tests showed that with the 2 drugs there was a particulary noticeable deficit in the most elementary of sensori-motor functions but only a negligible deficit of intellectual functions. On the other hand with the personality test used (MMPI), it was found that chlorpromazine had practically no effect whereas amobarbital brought about limited but distinct changes in the profile and particularly on the Ma, Sc and Mf scales. It is not possible to interpret precisely such modifications in the responses of subjects asked to describe their feelings and behaviour.

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Bibliographie technique

Les tests de Benton *(Visual R tention Test)*, de Cattell *(Culture Free test)* et de Porteus *(Maze Test)*, ainsi que le M.M.P.I. *(Minnesota Multiphasic Personality Inventory)* ont été utilisés dans l'édition française publiée par le Centre de Psychologie Appliquée — Paris.

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Effects of Chlorpromazine on Acquisition and Extinction of a Conditioned Response in Mice[1]

By

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With 1 Figure in the Text

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Several studies have recently established that chlorpromazine will affect the acquisition and extinction of a conditioned avoidance response in rats (ADER and CLINK 1957; MILLER et al. 1957; 1957a). ADER and CLINK (1957) used saline, 1.5 mgm./kgm., or 3.0 mgm./kgm. of chlorpromazine and found an increase in the number of trials required to learn an avoidance response as the dose level increased. *Ss* given 3.0 mgm./kgm. prior to extinction were found to extinguish the response most rapidly followed by the 1.5 mgm./kgm. group, with the placebo group being the most resistant to extinction.

MILLER et al. (1957) found more rapid extinction of an avoidance response as the dose level of chlorpromazine increased up to 1.25 mgm./kgm. They also found, by the use of a phenobarbital control group, that the more rapid rate of extinction was not a function of sedational effects or motor impairment brought about by the chlorpromazine. The square root of the number of avoidance responses during extinction was found to be linearly related to the log of the drug dosage.

In a subsequent study these same workers (MILLER et al., 1957a) tested one group of rats for extinction of an avoidance response shortly after injecting chlorpromazine. A second group was injected at the same time but not tested until five days later. Two corresponding saline groups were also employed. The group which was given the drug and tested shortly thereafter was found to extinguish the response most rapidly. No differences were found among the other three groups.

These studies employed the rat as the experimental animal and avoidance learning as the criterion for assessment of the effects of chlorpromazine. Since the results of these studies are thought to have

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implications for the therapeutic use of chlorpromazine on the human level (e.g., MILLER et al., 1957a), it seemed advisable to study another species and other responses to determine the limitations and generalities of previous findings. We used the mouse, a species phylogenetically close to the rat, but with a different behavioral repertoire.

DENENBERG (1958) has previously found that mice can learn to respond during the CS interval when given paired buzzer-shock trials in which the *S* always receives shock. When later tested for extinction, it was found that the mice gave a significant number of CRs prior to meeting an extinction criterion. This significant retention is presumably due to the "anxiety" arousing properties of the buzzer brought about by its association with shock during the prior conditioning. If this assumption is correct, it then follows that any procedure which acts to reduce *S*'s anxiety during the initial acquisition of the habit should manifest itself by more rapid extinction of the response on later testing. The specific hypothesis under investigation was that chlorpromazine, when given during acquisition training, should cause more rapid extiction of the response.

Method

Subjects. A total of 116 inbred male C57BL/6 mice from the Roscoe B. Jackson Memorial Laboratory were used. The *S*s were between five and six weeks of age when tested.

Procedure. Five *S*s were given acquisition training at the same time. Each *S* was placed into an individual compartment measuring $2^{3}/_{4}$ in. $\times$ $9^{1}/_{4}$ in. $\times$ 9 in. A constant current shock unit containing a 2.25 megohm resistor wired in series with the mouse was set at .5 ma. The *S*s were allowed 10 min. of habituation in the apparatus prior to the start of acquisition training. The training consisted of presenting a 3 sec. tone, which was always followed by 1 sec. of shock as soon as the tone terminated. After an intertrial interval of 41 sec., the tone was again presented followed by the shock. Twenty such trials were given each *S* in one session. No measures were taken of individual performance during the training interval. The typical response of the *S*s to both the US and CS was running. Jumping was the next more frequently observed response.

Five days later the *S*s were tested for retention of the CR by being given extinction training. *S*s were tested individually at this time. Each *S* was placed into the same shock unit as used during learning. The size of the test compartment was $4^{1}/_{2}$ in. $\times$ $14^{1}/_{2}$ in. $\times$ 9 in. After 10 min. of habituation, the tone was sounded for 3 sec., but no shock was given. Twelve sec. elapsed between the cessation of the tone and the presentation of the next tone. If *S* had not been quiet for at least five sec. prior

to the end of this intertrial interval, the next trial was delayed until *S* had ceased moving about the cage and had been quiet for five sec. If *S* either jumped, or ran a minimum of 7 in. during the interval that the tone was on, this was considered evidence of retention of the CR. The rationale here is that the same behavior occurred during acquisition training and it has also been found to hold true in other studies with the mouse (DENENBERG 1958). The procedure of 3 sec. tone followed by 12 sec. of quiet was continued until each *S* met an extinction criterion of no responses to three successive tones. This score was the dependent variable.

This procedure is a modification of one previously described in detail by DENENBERG (1958). Previous studies (DENENBERG 1958, 1959) have shown that this method of measuring extinction is a sensitive index of the organism's retention of the previously acquired habit.

Experimental Design. The basic experimental design was a 3×2 factorial. One hour prior to acquisition training 86 *S*s were randomly split into three groups and were given an intraperitoneal injection of either physiological saline, or 1.5 mgm./kgm. of chlorpromazine[1], or 4.5 mgm./kgm. of chlorpromazine in a volume of approximately 0.1 cc. One hour prior to extinction testing the *S*s in each of these three groups were randomly divided and injected with either physiological saline or 1.5 mgm./kgm. of chlorpromazine. In addition, 30 *S*s served to determine the operant response level to the tone. Fifteen of these mice were injected with saline and the other half received 1.5 mgm./kgm. of chlorpromazine. One hour later these *S*s were given the same extinction trials as described above. None of these *S*s jumped when the tone was presented, although running did occur.

Results

Table 1 presents the mean number of trials to meet the extinction criterion, the standard deviation, and the n for each of the groups tested. Since the n's differed slightly from group to group, an unweighted means analysis of variance was employed to evaluate the data. The two groups not given tone-shock acquisition training were compared to see whether the administration of chlorpromazine depressed the operant response level. The t ratio was less than one, indicating no motor impairment. These two groups were then compared with the six groups which were given tone-shock acquisition training. It was found that the groups receiving training took significantly longer to extinguish the response ($p < .05$) than did the controls. This finding indicates that the tone-shock conditioning procedure did lead to significant learning

[1] SMITH, KLINE, and French Laboratories generously supplied the Thorazine used in this study.

Table 1. *Summary statistics of extinction performance as a function of drug conditions present during acquisition and extinction*

Extinction Drug Rx		Drug Rx under Acquisition Training			
		Saline	1.5 mgm./kgm.	4.5 mgm./kgm.	Not trained
Saline	$\bar{x}$	4.20	4.47	3.08	2.07
	s	4.46	6.77	3.64	2.31
	n	15	15	13	15
1.5 mgm./kgm. .	$\bar{x}$	5.00	3.36	1.60	1.40
	s	5.02	3.00	2.13	2.29
	n	14	14	15	15

as measured by the extinction data. Within the groups given the tone-shock conditioning a significant linear dose response function was obtained ($p < .05$) with the groups receiving the high dose of chlorprom-

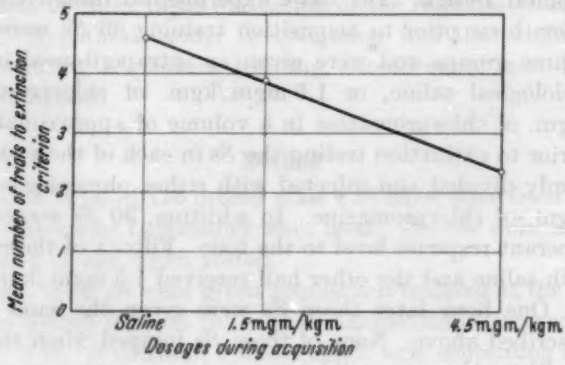

Fig. 1. Performance during extinction as a function of drug level present during acquisition

azine during acquisition extinguishing the response most rapidly. This relationship is shown in Figure 1, where the two extinction conditions are combined since they did not differ significantly. No difference in extinction behavior was obtained as a function of the dose levels injected prior to measuring extinction, nor was the Acquisition × Extinction interaction significant (both F ratios were less than 1). These latter findings indicate that the presence or absence of chlorpromazine during the measurement of extinction did not affect behavior, and that the effects of chlorpromazine during acquisition are independent of the effects of the drug during extinction for the levels studied.

Discussion

The finding of a significant linear dose response function, with the group which received the high dose of chlorpromazine during acquisition making the smallest number of extinction responses, supports the hypothesis that chlorpromazine during acquisition would lead to more

rapid extinction of an acquired anxiety response. It is important to note that performance during extinction was not affected by the immediately preceding drug injection nor by any interactive effects. At first glance, these findings appear to be in opposition to those of ADER and CLINK (1957), who found that rats given 1.5 mgm./kgm. of chlorpromazine prior to extinction testing had a more rapid rate of extinction than did the placebo group, but that the presence or absence of the drug during acquisition did not affect behavior. However, ADER and CLINK required that all their *Ss* reach the same learning criterion prior to initiation of extinction training. They found that the chlorpromazine group required significantly more trials then the placebo group to attain the criterion. In this study all *Ss* were given an equal number of trials during the acquisition session. Thus, our extinction criterion may be considered to be a direct measure of strength of learning. The data show that the chlorpromazine treated *Ss* did not acquire as strong a habit during the 20 trials as did the saline *Ss*. Thus, the data on acquisition of an avoidance response in the rat and acquisition of a conditioned response in the mouse are consistent.

The effects of chlorpromazine prior to extinction does not appear to be similar in the mouse and rat. Both ADER and CLINK (1957) and MILLER et al. (1957) have found that the administration of the drug prior to extinction leads to a more rapid rate of extinction. No effect was found in the present study. This suggests that the species and/or the response measures are critical parameters. The need for caution in generalizing the findings from one species to another until adequate comparative studies have been conducted is clearly indicated.

One interpretation that can be given to these data is that the chlorpromazine treatment reduced the "anxiety" level during acquisition. This reduction provided for a weaker association between tone and shock to be established, and resulted in easier extinction of the response. Other interpretations are possible. For example, the mice given drug treatment may not have had an opportunity to learn to run to the buzzer. A number of the mice which received the 4.5 mgm./kgm. dosage did not respond in as strong a fashion as the saline and 1.5 mgm./kgm. groups to the shock. Thus, if the *Ss* did not learn to run to the tone during acquisition, they would not be expeted to do so during extinction. However, the data of MILLER et al. (1957) with their phenobarbital control group tend to minimize this interpretation.

Summary

Mice acquired a tone-shock association under conditions of saline injections, or an injection of 1.5 mgm./kgm. or 4.5 mgm./kgm. of chlorpromazine. Five days later the *Ss* were tested for retention of the response by being given extinction trials. Each of the three groups were

divided and received either a saline injection or an injection of 1.5 mgm./kgm. chlorpromazine just prior to extinction testing.

A significant linear dose response function was obtained between amount of chlorpromazine injected during acquisition and performance under extinction, with the saline group requiring the greatest number of trials to extinguish. The presence or absence of chlorpromazine during extinction did not affect performance, nor was there any interaction between drug levels during acquisition and drug levels during extinction.

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Lithium in Psychiatric Therapy

Stock-taking after ten Years

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With 5 Figures in the Text

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Lithium salts were introduced into psychiatry at about the same time as the first organic ataractics (CADE; NOACK and TRAUTNER), but they have led a much more obscure existence and are still not very widely known or used. One of the explanations of this may probably be found in fear of their toxic effects, the nature and extent of which were largely unknown until recently. It may also have been of significance that lithium is of limited commercial interest as a drug and correspondingly little advertised. And finally, the somewhat narrower therapeutic range of lithium than of most other psychotherapeutic drugs may have weakened its ability to compete for the psychiatrists' attention.

It would, however, be unfortunate if a lack of more spectacular therapeutic properties should lead to a wholesale rejection of the psychiatric use of this drug. Clinical experience from the last decade has shown it to possess desirable therapeutic properties not shared by other therapies, and experimental work has shed new light on the mechanism of its toxic effects and thereby on their prevention.

It is therefore now possible to allocate to lithium treatment a place among the established therapeutic procedures, and the following is a survey and an evaluation of its present standing in practical psychiatric therapy. The general biology and pharmacology of the lithium ion have been reviewed elsewhere (SCHOU 1957).

Throughout this paper "lithium" refers to lithium ions and lithium salts; this is analogous with the general use in biological literature of "sodium" and "potassium" for the corresponding ions and salts.

Therapeutic Effects

Therapeutic Effect in Mania. Lithium has been used mainly against manic phases of the manic-depressive psychosis, and its effect in these cases is considered first. Table 1 is a summary of reports in the literature of manic patients treated with lithium and given no other physical therapy.

Table 1. *Reports on manic patients treated with lithium and given no other physical therapy*

Authors	Number of Patients					
	Total		Improved		Not Improved	
Cade (1949)	10		10		0	
Despinoy and de Romeuf (1951)	3		3		0	
Noack and Trautner (1951)	27		26		1	
Reyss-Brion and Grambert (1951)	4		3		1	
Deschamps and Denis (1952)	4		4		0	
Duc and Maurel (1953)	4		3		1	
Giustino (1953)	2		0		2	
Glesinger (1954)	7	21	5	15	2	6
Glesinger (1954)	14[1]		10		4	
Schou et al. (1955)	48		39[2]		9	
Sivadon and Chanoit (1955)	10		10		0	
Teulié et al. (1955)	25		20		5	
Gershon and Trautner (1956)	10[1]		9		1	
Rice (1956)	20	37	18	34	2	3
Rice (1956)	17[1]		16		1	
Andreani et al. (1958)	14		13		1	
Belling (1959)	32		24		8	
Schou, later material[3] (1959)	119		91		28	
	370		304		66	

[1] These groups were called "manic-depressive psychosis" (Glesinger; Rice) or "phasic psychosis" (Gershon and Trautner), but they appear to represent manic phases.

[2] The groups "+ effect" and "possible effect" (Schou et al. 1955) have been pooled.

[3] Patients treated during the period from the survey in 1955 until January 1959.

In the table are included all cases designated as mania, the typical ones as well as those with a more mixed picture in which mania was a dominant feature. Chronic as well as acute cases have been included and hypomanic states as well as fully developed manias. Excluded from the list are cases diagnosed as "excitation psychotique", "mixed psychosis", "schizo-affective state", and the like; nor are cases recorded in which lithium was given solely as a prophylactic against mania or exclusively as a maintenance treatment after an introductory series of electrostimulations (a not inconsiderable number in this hospital).

Under "Improved" are grouped all cases in which the treatment was accompanied by a significant decrease of the manic symptoms. In the cases listed under "Not Improved" lithium administration did not lead to any significant improvement of the condition, or it was accompanied by an aggravation; the latter course of events has, however, been observed so rarely that it must be considered without causal relation to the lithium treatment.

A list such as this can of course give only a very rough orientation, and its data must be evaluated with caution. It should be pointed out, for example, that the concept of mania presumably differs considerably among the authors; further, that the criteria for placing a case under "Improved" or under "Not Improved" may have varied from one author to another; and finally, that the treatment and observation periods differ considerably among the reports. In some of the larger materials the effect of the treatment was assessed 2—3 weeks after the start, but also other observation periods have been employed.

It appears from the table that a majority of the manic patients showed improvement during treatment with lithium. When the reservations mentioned above and the smallness of the materials are taken into consideration, there seems to be a fair agreement between the observations made by various authors. No difference in response has been noted between male and female patients or between young and old patients.

It has not been possible to subdivide the improved cases according to the degree of the improvement. The reports in the literature frequently fail to distinguish between "recovered" and "improved", and such a distinction is admittedly difficult for many of these, habitually often lively, patients. According to most authors between one half and two thirds of the patients grouped under "Improved" in table 1 appear to have become symptom-free, i.e. "recovered", during the treatment, while the remaining cases showed varying degrees of improvement.

The question now arises how many of these about 80 per cent cures and improvements are caused by a pharmacological action of lithium and how large a fraction is due to the effect of such unspecific factors as suggestion and spontaneous variation. It is no more possible in the case of lithium than in the case of other therapies of mania to obtain an exact quantitative measure of the specific pharmacological efficiency; but it appears from table 1 that the frequency of improvements does not exceed about 80 per cent, and this figure must consequently represent the maximum therapeutic efficiency. It has also been possible, through a careful planning of the therapeutic experiment, to get an estimate of the minimum efficiency. Schou et al. (1954, 1955) carried out a controlled double-blind experiment in which neither the patients nor the observers were told whether the tablets given contained lithium or were placebos. The effect of the treatment was evaluated with due consideration of the pre-treatment course of the disease in each case. Out of a total of 48 manic patients 39 could be classified as "Improved" (cf. table 1), and these 39 cases were subdivided into "+ effect" and "possible effect" according to whether it could be considered highly probable that the improvement

was caused by lithium and by lithium alone, or whether an improvement due to other causes could not be excluded. Cases classified as "+ effect" fulfilled one or more of the following criteria: a) in a patient with manic attacks occuring at regular intervals, lithium treatment was able to prevent these attacks (fig. 1); b) in a patient with a very protracted mania, the intensity of the manic symptoms decreased during administration of lithium and increased during placebo periods

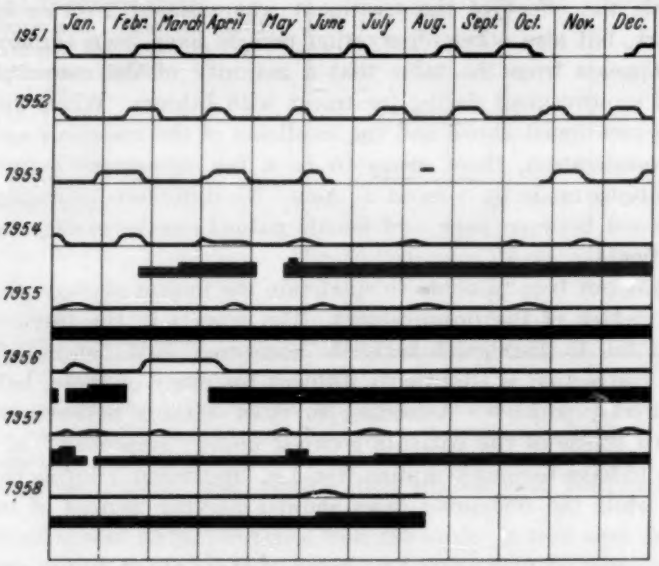

Fig. 1. Man, born in 1902. At 23 and at 30 depressions of short duration. From the age of 31 been in mental hospital with periodic mania; no depressions. Treatment with lithium carbonate was started in February 1954. His manic attacks have not disappeared completely, but they are much less intense than previously. The patient is now in a quiet ward and has ground parole

(fig. 2); c) in a patient with a mania that changed rapidly and fortuitously in intensity before treatment, continued lithium treatment was accompanied by a neutral period that was significantly longer than the spontaneous neutral phases (fig. 3); and d) in a patient with previous manic attacks of very regular duration, lithium treatment brought about a significant shortening of the phase (fig. 4). All cases in which lithium administration led to improvement, but in which not at least one of these criteria was fulfilled, were classified as "possible effect". It should be noted that the distribution of patients among the two groups was independent of the degree of improvement; recovered as well as improved cases were found in both groups.

The study showed that of the 39 improved cases 18 could be grouped under "+ effect" and 21 under "possible effect", and the authors where therefore led to conclude that in *at least* half of the improved cases,

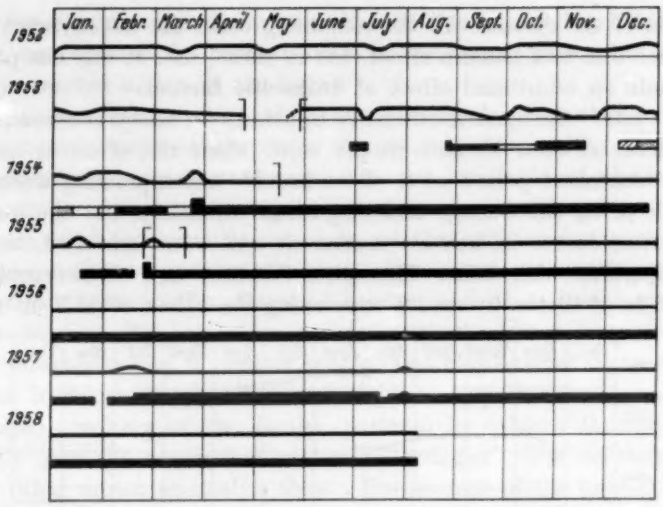

Fig. 2. Woman, born in 1886. At 22, at 52 and at 54 irregular phases of depression and mania. From the age of 62 in mental hospital with chronic mania. Lithium treatment was started in 1953 as a double-blind experiment (black: lithium carbonate; hatched: lithium citrate; dotted: lithium chloride; white: placebo). She could be discharged in May 1954 and has since then, on a maintenance treatment, been almost continuously mentally normal and out of hospital

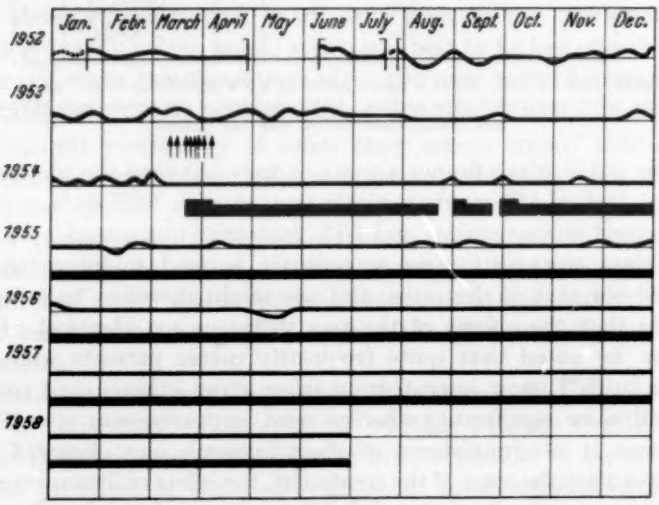

Fig. 3. Man, born in 1918. He has been in mental hospital almost continuously for the last 12 years with a condition that has changed irregularly between neutral or slightly depressed phases and brief, intense manic periods. Only transient effect of electric convulsive therapy (arrows). Treatment with lithium carbonate was started in March 1954. The patient is still in hospital, but he is no longer psychotic and will be discharged as soon as he has become sufficiently resocialized after his long hospital confinement

the improvement must have been due to a pharmacological effect of the lithium ion and could not be ascribed to suggestion or spontaneous

variation of the disease. In the remaining cases the improvement *may* have been due to a lithium effect, but in these cases it was not possible to exclude an additional effect of unspecific factors.

The "true" therapeutic efficiency of lithium in mania is consequently somewhere between 40 and 80 per cent, when the effect is assessed after a treatment period of 2—3 weeks. No corresponding account is available of its short-range and long-range efficiency, but the question of the time factor in lithium treatment will be commented on later.

Comparison with Other Therapies. SCHIELE and SCHNEIDER summarized in 1949 the literature concerning the effect of ECT in mania,

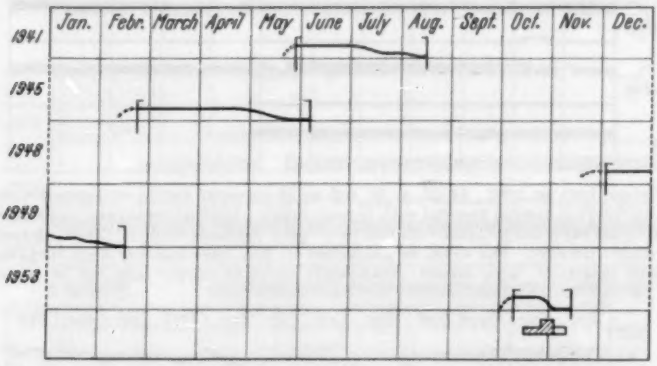

Fig. 4. Woman, born in 1904. At 34 a manic period of a few months duration. At 38, 42 and 45 manic phases, which each lasted three months. At 49 again manic and treated with lithium citrate; this manic phase lasted only one month

and later publications do not appear to have changed the picture significantly. Out of 466 manic patients treated with ECT 62% recovered, 18% showed improvement, and 20% remained unchanged. Both ECT and lithium treatment seem accordingly to lead to improvement in about 80 per cent of the cases, and one might therefore be tempted to conclude that the effects of the two therapies are identical. It may, however, be noted that quite frequently manic patients who do not respond to ECT show improvement when given lithium, and *vice versa*. And still more sign ficant: whereas most improvements after ECT, at least when it is administered at short intervals, are observed around 3—6 days after the start of the treatment, the effect of lithium treatment sets in more gradually and usually does not reach its maximum until the 6th—10th day. It is furthermore a general experience that most improvements obtained by treatment of mania with ECT are of very limited duration, usually around 2—3 weeks; lithium therapy, on the other hand, may be given as a maintenance treatment for long periods, and it is therefore particularly useful in cases of protracted or frequently recurring mania. It is often possible to take advantage of this differ-

ence between the two therapies: when ECT is followed by lithium treatment, one obtains the prompt effect of the former in combination with the protracted action of the latter.

During recent years manic excitation has been treated extensively with organic psychotherapeutic drugs and often with good results. Unfortunately only few observations are available of the effects of these drugs and of lithium in identical or comparable groups of manic patients, and the question of their relative efficiencies in mania still awaits a definitive answer. One may, however, note certain qualitative differences between the effects of lithium and of, e.g., chlorpromazine and reserpine. While patients treated with the latter drugs frequently are characterized by a certain apathy and may exhibit signs of Parkinsonian hypokinesia (facial immobility) or hyperkinesia (smacking of the lips, gnashing of the teeth), patients in lithium therapy do not usually give the impression of being "drugged"; nor do they usually show other motor anomalies than a fine tremor of the hands. A difference between the therapeutic effects is also indicated by the observation that in patients with atypical mania, who in addition to the manic symptoms present pronounced paranoid traits, treatment with a combination of chlorpromazine and lithium often leads to better results than those obtained with either drug given alone. Lithium appears to act primarily on the manic symptoms and to be less effective against delusions, while the opposite is often the case with chlorpromazine.

Therapeutic Effect in Non-Manic Excitation. Lithium has also been used against excitations of other than manic origin; but controlled therapeutic experiments have not been performed, and statements about the efficiency of the treatment are somewhat vague. A single author (GLESINGER) finds lithium even more effective in non-manic excitation than in mania, whereas according to most other authors lithium acts rather specifically against manic symptoms, but may also be of some therapeutic value against the affective element in other excitations.

Therapeutic Effect in Depression. It is strange that the — theoretically so important — question of whether lithium is effective also against depression has been given so little attention by those who have studied its effect in the manic phases of manic-depressive psychosis. Possibly the early experiences discouraged further studies. While CADE found that lithium neither helped nor aggravated depression, NOACK and TRAUTNER noted that some of the depressed patients became worse during the treatment. But they did not indicate the extent of the experience on which this statement was based.

One of the patients described by SCHOU et al. (1954, 1955) had very regular shifts between manic and depressive phases. When lithium

was administered, one could observe a reduction of the intensity of not only his manic but also of his depressive symptoms; he did not, however, at any time become symptom-free. This observation led to a more systematic study of the effect of lithium in endogenous depression (HANSEN et al.), executed exactly as the one performed previously with manic patients. Only in one out of twelve patients thus treated did the condition change synchronously with the medication: improvement during lithium periods and aggravation during placebo periods. But when lithium was administered to this patient during subsequent depressive phases, it was without any beneficial effect. The clinical changes observed in the eleven other patients could not with any probability be ascribed to lithium; administration of the drug resulted neither in improvement nor in aggravation of the depressions.

In view of this rather clear-cut negative result, it is note-worthy that ANDREANI et al. found improvement in 10 out of 24 depressed patients during treatment with lithium. Since the therapeutic experiment was not a controlled one, it is difficult to estimate the extent to which spontaneous variation may have been responsible for these improvements; but the Italian observation indicates that the question of a possible prophylactic or therapeutic value of lithium against depression has not yet found a final answer.

Toxic Effects

The toxic properties of the lithium ion have during the last century attracted interest intermittently; but the gravity of the risk involved in an uncontrolled consumption of lithium salts was not fully realized until the late 1940'ies, when several fatal lithium intoxications occurred in cardiac patients who used lithium chloride as a substitute for sodium chloride in their food (CORCORAN et al.; HANLON et al.).

Later clinical and experimental work has led to a better understanding of the point of attack and the mechanism of the toxic action of lithium, and it seems beyond doubt that at least some of these fatalities might have been avoided, if one had then known what we now know about lithium intoxication. The toxicological literature on lithium up till 1956 was reviewed in the paper referred to above (SCHOU 1957); later studies have yielded further information on important points (HERKEN et al.; SCHOU 1958a, b, c; TRAUTNER et al.).

Toxic Signs and Symptoms. Diarrhea and vomiting are often early toxic signs. Though unpleasant, these troubles are, however, rarely dangerous, and they disappear in most cases within 1—2 days when the lithium dosage is reduced temporarily.

A fine tremor of the hands is extremely frequent and may be observed even in patients who receive very small lithium doses. When

present in slight degree it must be considered entirely innocuous. If, on the other hand, the tremor becomes so pronounced that it interferes with the patients' eating or needlework, or if the lower jaw also starts to tremble, one may usually take these symptoms as a warning that the lithium concentration in blood and tissues is about to reach toxic levels. The serum lithium concentration is in these cases usually around or above 2 meq./l, and the patients frequently exhibit additional neurological anomalies such as drowsiness, mild ataxia, giddiness, and possibly tinnitus and blurred vision. Other symptoms of impending intoxication are thirst and a large output of dilute urine.

If lithium intoxication proceeds further, the clinical picture becomes very complex and may involve several organs and organ systems. Confusion, fasciculations, hyper and hyporeflexia, re-occurrence of diarrhea and vomiting, nystagmus, seizures, and coma have all been described in the literature. Grave lithium intoxications in man are usually accompanied by serum lithium concentrations around 3—4 meq./l; if the latter reach values of 4—6 meq./l, the intoxication runs in most cases a fatal course.

There is a certain inter-individual variation of the tolerance to lithium, and one may occasionally come across abnormally sensitive patients, who exhibit signs of lithium intoxication at serum lithium concentrations around 1.0—1.5 meq./l. But they are exceptions.

Also other toxic manifestations than the ones listed above may be observed occasionally. Electrocardiographic changes (flattening or isoelectricity or in a few cases inversion of the T waves) occur in about 20 per cent; the patients do not usually show any other signs of intoxication, their serum lithium concentration is mostly below 2 meq./l, and their serum potassium value is inside the normal range. Also electroencephalographic changes (appearance of frequencies of 6—7 c.p.s. and an increase of the voltage) may be noted, and lithium treatment has in a few cases given rise to visual and tactile hallucinations (Bleuler; Hastrup).

Pathology and Patho-Physiology. Experimental work with animals has shown that the principal toxic action of lithium is on the kidney function (Radomski et al.; Schou 1958a, b). In less severe intoxications the picture resembles diabetes insipidus with hyposthenuria and a pronounced polyuria, but the excessive excretion of urine is unaffected by even large doses of antidiuretic hormone. One must therefore suppose that the condition is due to a direct injury at the sites of active tubular reabsorption of water, i.e., that it is a "water-losing nephritis" of toxic origin. It is completely reversible.

If a graver intoxication is produced by an increase of the lithium dosage (or by a reduction of the sodium intake, see later), the excretory

function of the kidneys suffers a complete breakdown. The animals become oliguric or anuric and develop azotemia, and lithium is accumulated in the organism. This condition is no longer reversible, and it is histologically characterized by degenerative changes in the kidney tubules.

It may be asked whether the experience from animal experiments may be applied to humans. Metabolic and histological information is frequently incomplete in the published reports of lithium intoxication in man, and it is difficult to get a clear picture of the patho-physiology and, in the fatal cases, the cause of death. In some of the latter cases no mention is made of an impaired renal function; in others, oliguria and azotemia have been noted as pre-terminal phenomena. Presumably the psychiatrist having patients in lithium therapy should be on guard primarily against kidney damage but at the same time keep in mind the possibility of other toxic actions.

Prevention of Lithium Intoxication. Lithium intoxication may be prevented, firstly, by excluding from treatment patients who suffer from renal disease or from affections which, directly or indirectly, threaten the kidney function. Secondly, the patients must be under surveillance during the treatment so that lithium administration can be stopped on the appearance of such signs and symptoms of impending intoxication as, e.g., a pronounced tremor of the hands, drowsiness, ataxia, persistent diarrhea or vomiting, thirst, and excessive excretion of urine. Regular control of the lithium concentration in the blood is also of value as a guide for the therapy; if the serum lithium concentration exceeds 2 meq./l, the lithium dosage should be reduced. The serum lithium concentration may be determined by means of a sufficiently sensitive flame photometer (e.g., a Beckman DU spectrophotometer with photomultiplier and flame attachment). The determination is simple and rapid.

And finally, not only must the patients' lithium dosage be under control, but one must also make sure that their sodium intake is sufficient and remains sufficient during the treatment. The unfortunate experience gained from substitution of lithium chloride for sodium chloride in the diet, served to indicate that there might be an inverse relation between sodium intake and the toxicity of lithium. This has later been confirmed both qualitatively and quantitatively in experiments on animals. A high sodium intake protects against the tubulo-toxic action of lithium, presumably through a competition between the two ions for entrance into and re-absorption through the tubule cells (Schou 1958a, b). Animals with a high sodium intake excrete lithium more efficiently and maintain with the same lithium dosage a lower lithium concentration in blood and tissues than do animals kept on a sodium-

poor diet (fig. 5). It is therefore of prime importance that the amount of sodium consumed by patients in lithium treatment does not at any time become too low. Whenever it is in danger, whether because of intercurrent disease or refusal to eat or for some other reason, the lithium dosage must be reduced, or the patients must have an extra supply of sodium.

One may of course also protect the patients by giving them a constant extra supply of sodium chloride. Since the therapeutic effect of lithium presumably depends on a certain lithium concentration in the tissues and since an increase of the sodium intake leads to a decrease of the lithium concentration in blood and tissues, it is under these circumstances necessary to raise the lithium dosage slightly; but this should in no way endanger the now well-protected kidney tubules. In this hosital an extra supply of sodium chloride has not been considered necessary as a general measure; but tablets containing lithium and sodium in equivalent amounts have been administered with advantage to patients who were unusually liable to accumulate lithium when treated with the ordinary lithium carbonate tablets.

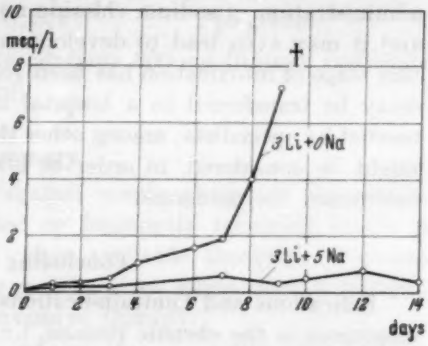

Fig. 5. Average serum lithium concentration in two groups of rats, which both were treated with 3 meq. lithium/kg body weight/day, and which had sodium intakes of 0 and 5 meq./kg/day, respectively. Blood samples were drawn 24 hours after each intraperitoneal injection of isotonic lithium chloride

Treatment of Lithium Intoxication. We are on much less safe ground when it comes to the treatment of manifest, severe lithium intoxication. A number of therapeutic procedures suggested in the literature seem either to lack a rational foundation (administration of dimercaprol, laxatives, diuretics, hexamethylene tetramine, and adrenocortical hormones) or merely to support the patients' general condition (administration of fluid, calories, and vitamines). COATS et al. claim a beneficial effect of potassium in cases of lithium intoxication, but it is difficult to evaluate the efficiency of the therapy because a control material is lacking.

From the experience with animals the rational treatment of a patient with incipient lithium intoxication would appear to be the administration of large amounts of sodium, e.g. 5—15 grams sodium chloride per day. This leads to an acceleration of the renal elimination of lithium and a consequent lowering of the lithium concentration in

blood and tissues. In this hospital cases of impending lithium intoxication have during the last 2—3 years been treated with large amounts of sodium chloride with good results; but the material is small, and a comparable material of un-treated patients or of patients given other therapy is admittedly not available.

There is a proviso concerning the use of sodium against lithium poisoning. If the intoxication is so far advanced that the patient, in spite of a sufficient supply of fluid, has developed oliguria or anuria, administration of sodium chloride no longer serves any useful purpose, and it may even lead to development of brain or lung edema. When this stage of intoxication has been reached, the patient should without delay be transferred to a hospital in which his renal failure may be treated by specialists; among other therapeutic measures a hemodialysis might be considered, in order to lower the lithium concentration and counteract the azotemia.

Concluding Remarks

Indications and Contraindications. The main indication for lithium treatment is the chronic manias, i.e. the cases with protracted or frequently recurring mania. This is a rather small group of patients, but very often these cases have proved resistant to most other therapies, and lithium treatment seems to offer the patients a very fair chance of either considerable improvement or total recovery, which they would not otherwise have had. It is often practical to stop the manic attack by means of a series of electrostimulations and then maintain the improvement by a continued lithium medication. We have given lithium to patients continuously for more than four years without any signs of late side effects and without any decline of the therapeutic efficiency of the drug.

As absolute contra-indications against lithium treatment must be regarded a) renal disease, b) severe vascular and cardiac disease, and c) conditions with an insufficient sodium intake. Cautiousness with lithium administration must be advocated in a) patients with a failing general health, b) patients with epilepsy and/or abnormal electroencephalogram, and c) very old patients.

Administration and Dosage. Lithium is administered orally, usually as the carbonate (the chloride is too hygroscopic and the citrate too bulky). Each tablet may contain, e.g., 300 mg lithium carbonate, which corresponds to a lithium content of 56 mg or 8 meq. The initial dosage is usually around 4—7 tablets per day, depending on the size of the patient; after a week or so the dosage may often be reduced, and a maintenance dosage of 2—4 tablets per day is usually adequate.

The maintenance dosage must in each case be adjusted in accordance with the therapeutic effect, the possible occurrence of side effects, and the serum lithium concentration, which should be kept below 2 meq./l.

In the few instances in which patients prefer a liquid preparation, one may prescribe the following mixture:

Lithium Carbonate	2 grams
Acacia Mucilage, U.S.P.	10 grams
Glycyrrhiza Fluidextract, U.S.P.	5 grams
Peppermint Water, U.S.P.	85 grams.

This is quite palatable, and it contains 300 mg lithium carbonate (= 1 tablet) per tablespoon (15 ml).

Summary

Lithium therapy is effective against manic phases of the manic-depressive psychosis; in protracted or frequently recurring mania it seems to offer advantages over other available therapies. Lithium salts are administered orally; they may be given alone or as a maintenance treatment after electric convulsive therapy.

Lithium is potentially toxic, and overdosage may lead to injury of the kidney tubules. A high sodium intake accelerates renal elimination of lithium and serves to protect the organism against intoxication.

Patients suffering from renal or cardiac disease should not be given lithium. In patients receiving lithium the dosage must be regulated according to individual tolerance, and one must make sure that the sodium intake is sufficient and remains sufficient. The patients should be supervised clinically and biochemically.

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DR. SCHWARZ sanol PRÄPARATE

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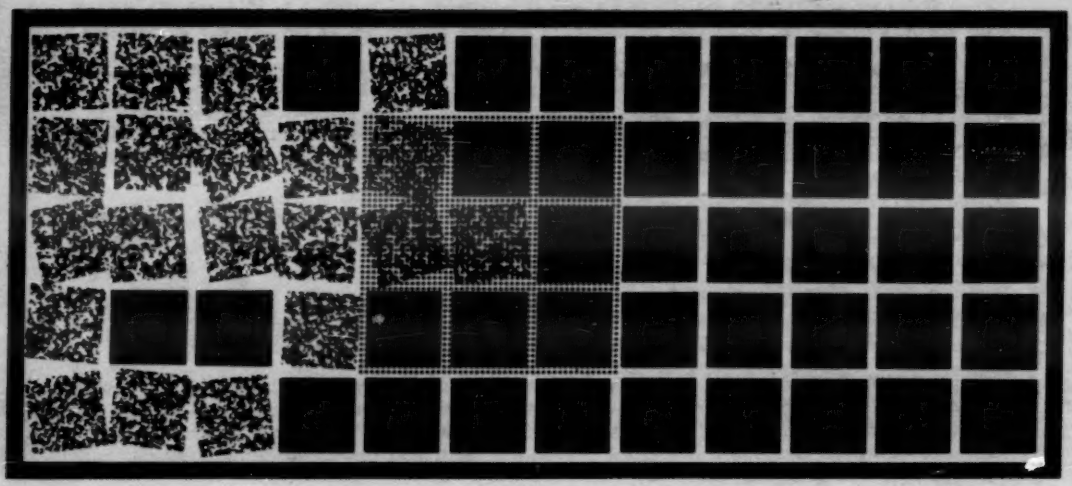

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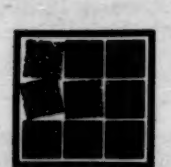

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